REMARKS

A check for $510 for the fee for a three-month extension of time accompanies this response. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050.

Although already made of record, the Examiner's attention is directed to co-owned allowed U.S. application Serial No. 09/271,575, now U.S. Patent 6,602,274 and allowed U.S. application Serial No. 09/905,501; and co-pending U.S. application Serial Nos. 10/317,269; 10/410,700; 10/802,284; and 09/386,692. These applications were made known to the Office in Information Disclosure Statements, filed March 18, 2003, July 30, 2003 and June 22, 2004.

The title of the application is amended herein to more distinctly describe the subject matter. Basis for the amendment can be found throughout the specification (for example, see paragraph [013]).

Claims 1-6, 11, 12, 16-24, 36 and 38-56 are presently pending in this application. Claim 46 is amended herein to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (for example, see paragraphs [018] and [047]). Claims 50-56 are added herein. Basis for added claims 50 and 51 can be found throughout the specification (for example, see paragraph [044]). Basis for added claim 52 can be found throughout the specification (for example, see original claim 1 and claim 22 and paragraphs [032], [036] - [043 and [047] - [050]). Basis for added claims 53, 54 and 55 can be found throughout the specification (for example, see originally filed claims 2, 3 and 4, respectively). Basis for added claim 56 can be found throughout the specification (for example, see paragraph [048]. No new matter is added. Accordingly, entry of the amendments to the claims is respectfully requested.

REJECTION OF CLAIMS 1-6, 11, 12, 16-24, 36 AND 38-49 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-6, 11, 12, 16-24, 36 and 38-49 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter commensurate in scope with these claims. The Examiner alleges that the specification (1) provides insufficient guidance as to how to make all "derivatives" of benzoporphyrin, bacteriochlorophyll and "ether analogs" because no

chemical structure is provided; (2) provides insufficient guidance as to binding specificity of the targeting moiety and thus it is unpredictable which targeting moiety will target to abnormal endothelium in the eye; and (3) provides insufficient guidance as to the intensity of light to be used.

This rejection is respectfully traversed. The previous response, mailed June 16, 2004, is incorporated by reference herein in its entirety. The Examiner also provides a list of embodiments that she considers to be enabled by the specification. It is respectfully submitted that claims 52-56 added herein recite such embodiments, and, hence are outside the purview of this rejection.

RELEVANT LAW

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. The "invention" referred to in the enablement requirement of section 112 is the claimed subject matter. *Lindemann Maschinen fabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or

> accuracy of any statement in a supporting disclosure and to back up assertions of its own with evidence or reasoning which is inconsistent with the contested statement.

Id. (emphasis in original); See also *Fiers v. Revel*, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993); *Gould v. Mossinghoff*, 229 USPQ 1, 13 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. § 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct"). A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). It is incumbent upon the Examiner to first establish a *prima facie* case of non-enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim ... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. See *Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ("patents are written by and for skilled artisans"). To hold otherwise would require every patent document to include a technical treatise for the

unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement of patent disclosures. See *Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999) ("The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel."); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983) ("Patents are written to enable those skilled in the art to practice the invention, not the public.")

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The PTO has promulgated guidelines, which incorporate the above-noted law, for examining chemical/biotechnical applications with respect to 35 U.S.C. §112, first paragraph, enablement. As set forth in the guidelines, the standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988). In determining whether any experimentation is "undue," consideration must be given to the above-noted factors.

As indicated in the published guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

THE CLAIMS

Claim 1 is directed to a method to treat neovascular disease of the eye that includes administering a conjugate including a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound; where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Claims 2-6, 11, 12, 16-24, 36 and 42 depend from claim 1 and are directed to various embodiments thereof.

Claim 46 is directed to a method to treat neovascular disease of the eye that includes administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovascular tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged, where the neovascular tissue is treated with a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2. Claims 47-49 depend from claim 46 and are directed to various embodiments thereof.

ANALYSIS

The claimed subject matter is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes administering a conjugate including a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovasculature tissue; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target

tissue; and illuminating the neovasculature target tissue with light including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue, where a combination of an intensity of light used for the step of illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. In this instance, applicant is providing a general method of photodynamic therapy to treat neovascular disease of the eye that includes a conjugate of photosensitizing agents and targeting moieties, which are known elements. It is the instant applicant that discloses that in conducting photodynamic therapy, there are combinations of the parameters of light intensity and duration of irradiation that can be selected, which, when used in conjunction with a targeted photoreactive compound, provide for a total fluence that achieves destruction of the target tissue without damage to a non-target tissue through which the light passes.

A. Enabling Disclosure

The Examiner states that the specification **is enabling** for the method to treat neovascular disease of the eye including administering a targeted photo-sensitizing compound selected from among chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, porfimer sodium, δ-aminolevulinic acid protoporphyrin, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins, pyropheophorbide compounds, and verteporfin conjugated to a targeting moiety selected from among VEGF ligand, VEGF receptor, antibody or antibody fragment that binds to VEGF receptor, a complete or functional bindable fragment of human antibody L19, αvβ3 integrin, the extra-domain B of fibronectin or carcino-embryonic antigen (CEA); allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound; where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. The Examiner

further states that the specification is enabling for the method where the light is non-coherent light or coherent light; where the photosensitized neovascular tissue is illuminated for a time interval of between 4 minutes and 72 hours; where the photosensitized neovascular tissue is illuminated for a time interval of between 60 minutes and 148 hours; where the neovascular tissue is treated with a total fluence of light irradiation from between about 30 J/cm^2 to about 25,000 J/cm^2; and where the conjugate is incorporated into a liposomal preparation (see Office Action pages 2-3).

B. Alleged Need for Undue Experimentation

The Examiner states that the exemplary steps are enabled but are allegedly not commensurate in scope with the claims. First, the Examiner alleges that the specification provides insufficient guidance to make all "derivatives" of benzo-porphyrin, bacteriochlorophyll and "ether analogs" because no chemical structure is provided. As discussed below, application respectfully disagrees. First, photosensitizing agents are well known to those of skill in the art and are reagents used in the methods. There is no need to teach how to make such well known compounds. Second, it is alleged that insufficient guidance as to the binding specificity of the targeting moiety is provided. Again, as discussed below, such targeting moieties and their respective specificities are known to the skilled artisan.

Finally, the specification allegedly provides insufficient guidance as to the combination of the intensity of light used for the illumination and the duration of illumination to arrive at the total fluence effective for treating neovascular disease without impairing or destroying other tissues because there is allegedly insufficient guidance for the intensity of light to be used. The Examiner concludes that one of skill in the art would not be able to practice the claimed methods without an undue amount of experimentation. Applicant respectfully submits that it would not require undue experimentation to use the claimed methods in the treatment of neovascular disease of the eye for the following reasons.

1. Teachings in the Specification

a. The Structure of Photosensitizing Compounds

The Examiner alleges that there is insufficient guidance as to the structure of photosensitizing compounds such as benzoporphyrin "derivative," bacteriochlorophyll "derivative" or "ether analogs" conjugated to targeting (Office Action, page 9). The

Examiner alleges there is insufficient guidance as how to make all "derivative" of benzoporphyrin, bacteriochlorophyll and "ether analogs" without the chemical structure. The Examiner alleges that there is insufficient guidance as to which part of the derivatives of benzoporphyrin or bacteriochlorophyll or "ether analogs" can be modified and still retain its function (see Office Action, page 10). Applicant respectfully disagrees.

i. Benzoporphyrin Derivatives

The Examiner alleges there is insufficient guidance as how to make all derivatives of benzoporphyrin without providing the chemical structure. As a preliminary matter, applicant respectfully submits that the claims include as subject matter "benzoporphyrin derivatives" and not "derivatives of benzoporphyrin" as alleged. At the time of the effective filing date of the claims, the recitation "benzoporphyrin derivatives" (BDPs) was known to those of skill in the art to refer to a subset of porphyrins useful in photodynamic therapy (for example, see Liu, U.S. Pat. No. 5,053,423; Chang *et al.*, U.S. Pat. No. 5,064,952; Gulliya *et al.*, U.S. Pat. No. 5,091,385; and Allision *et al.*, U.S. Pat. No. 5,214,036). The methodology for BPDs is known in the art (for example, see Gulliya *et al.*, U.S. Pat. No. 5,091,385and Pangka *et al.*, J. Org. Chem. 51:1094-1100 (1986). A. M. Richter *et al.* ("Benzoporphyrin and Benzoporphyrin Derivatives (BPDs)," J. Natl. Cancer Inst. 79:1327-32 (1987)) discloses preliminary studies on the phototoxicity of BPDs (see also A. M. Richter *et al.*, Proceedings of SPIE--The International Society for Optical Engineering, 997:132-38 (1988)). Kessel (Photochem. Photobiol. 49:579-82 (1989)) examined *in vitro* photosensitization with a BPD.

The applicant respectfully submits that a patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). As demonstrated by the references cited above as well as others in this art and those already made of record, benzoporphyrin derivatives, their structures and methods of making BPDs were well known in the art at the time of the effective filing date of the claims.

Further, methods of conjugating benzoporphyrin derivatives to ligands reactive with a target were known in the art. For example, Richter *et al.* (U.S. Patent No. 5,945,439 (1999)) teaches conjugating BPDs to specific ligands reactive with a target, such as receptor-specific ligands. It is further submitted that conjugating binding pairs

to photosensitizing compounds was also known to those of skill in the art at the time the application was filed (for example, see Fritzberg *et al.*, U.S. 5,976,535 (1999); Davalian *et al.*, U.S. 5,616,719 (1997); and Pease *et al.*, U.S. 5,618,732 (1997)). Applicant respectfully submits that there is sufficient guidance in the specification in light of what is known in the art at the time of the effective filing date of the claims that the skilled artisan can make a conjugate including a benzoporphyrin derivative for use in the claimed method without undue experimentation.

Thus, applicant respectfully submits that benzoporphyrin derivatives, the structures of benzoporphyrin derivatives, methods of making benzoporphyrin derivatives and method of conjugating benzoporphyrin derivatives to targeting moieties were well known in the art at the time of the effective filing date of the claims. It would not have required undue experimentation to make and use conjugates including benzoporphyrin derivatives in the claimed methods in light of the specification and what was known in the are at the effective filing date of the claims.

ii. Alkyl Ether Analogs

The Examiner alleges that there is insufficient guidance in the specification as to how to make all "ether analogs" without the chemical structure (see Office Action page 5). Applicant respectfully submits that the claims include as subject matter embodiments where the photosensitizer compounds in the conjugates are "alkyl ether analogs of chlorins" (see, for example, claim 42). Alkyl ether analogs of chlorins were well known in the art at the time of the effective filing date of the claims, and the application directs the skilled artisan to exemplary art. For example, at page 11, paragraph [040], the specification directs those skilled in the art to Pandey *et al.* (U.S. Pat. No. 5,952,366 (1999), entitled "Alkyl ether analogs of chlorins having an N-substituted imide ring"). This art is incorporated by reference in its entirety in the instant application. Pandey *et al.* teaches the structures of the alkyl ether analogs of chlorins and methods for preparing the compounds. See also U.S. Pat. Nos. 5,591,847; 5,770,730; 5,864,035; Pandey *et al.*, Photochem. Photobiol. (1991) 53: 65; and Pandey *et al.*, Photochem Photobiol. (1996) 64:194-204.

Further, methods of conjugating chlorins to targeting moieties to specifically target the photosensitizing compound were known in the art. For example, Rakestraw *et al.* teaches conjugating a chlorin via covalent bonds to monoclonal antibodies (Rakestraw *et al.*, *Proc. Nat. Acad. Sci. USA 87*: 4217-4221 (1990).

Sternberg *et al.* (*Tetrahedron 54*: 4151-4202 (1998)) teaches conjugating porphyrins to biomolecules including antibodies, steroids, sugars, and polynucleotides. Fritzberg *et al.* (U.S. 5,976,535 (1999)) teaches conjugating cytotoxic agents to one member of a ligand/anti-ligand binding pair, and teaches conjugation to a receptor, an oligonucleotide, an enzymatic substrate or other binding site present on or in the target cell population.

Thus, applicant respectfully submits that the specification provides sufficient guidance in light of what is known in the art at the time of the effective filing date of the claims that the skilled artisan can make a conjugate that includes an alkyl ether analog of chlorin as the photosensitizing compound for use in the claimed methods without undue experimentation.

iii. Bacteriochlorophyll Derivatives

The applicant respectfully submits that bacteriochlorophyll derivatives were well known in the art at the time of the effective filing date of the claims, and the application directs the skilled artisan to exemplary art. For example, at page 11, paragraph [040], the specification directs those skilled in the art to Scherz *et al.* (U.S. Pat. No. 5,955,585 (1999), entitled "Catalytic condensation method for the preparation of chlorophyll and bacteriochlorophyll derivatives"). This art is incorporated by reference in its entirety in the instant application. See also U.S. Pat. Nos. 5,864,035; 5,744,598; 5,726,169; 5,650,292 and 5,424,305; and Rosenbach-Belkin *et al.*, Photochem Photobiol. (1996)64(1):174-81; and Henderson *et al.*, J Photochem Photobiol B. (1991) 10(4):303-13.

Further, methods of conjugating bacteriochlorophyll derivatives to targeting moieties to specifically target the photosensitizer were known in the art. For example, Scherz *et al.* (U.S. Pat. No. 5,955,585) teaches conjugating bacterio-chlorophyll derivative with cell-specific ligands, such as hormones, growth factors or tumor-specific antibodies, in order to deliver the compounds more selectively to a tumor site.

Thus, applicant respectfully submits that the specification provides sufficient guidance in light of what was known in the art at the time of the effective filing date of the claims that the skilled artisan can make a conjugate that includes a bacterio-chlorophyll derivative as the photosensitizing compound for use in the claimed methods without undue experimentation.

b. Selection of a Photosensitizing Compound

The specification provides a detailed amount of direction and guidance for selection of a photosensitizing compound that is encompassed in the claims. For example, paragraph [036] discloses that

> a photosensitizing compound is a chemical compound which homes to one or more types of selected target cells and, when contacted by radiation, absorbs the light, which results in impairment or destruction of the target cells. Virtually any chemical compound that homes to a selected target and absorbs light may be used in this invention. Preferably, the chemical compound is nontoxic to the subject to which it is administered or is capable of being formulated in a nontoxic composition. Preferably, the chemical compound in its photodegraded form is also nontoxic.

The specification teaches that the photosensitizing compound generates singlet oxygen and/or other reactive species when the photosensitizing compound absorbs light at a wavelength which closely matches the absorption spectra of the photosensitizer (paragraph [005]), which results in impairment or destruction of the target cells (paragraph [036]). The function of a photosensitizing compound in photodynamic therapy is well known to those skilled in the art (for example, see Dougherty *et al.*, *Proc. Int. Symp. Porphyrins Tumor Photother.*, Milan, 16-18 May 1983; Sternberg *et al.*, *Tetrahedron 54*: 4151-4202 (1998)).

The specification teaches that the photosensitizing compound absorbs light in the range of 500 nm - 1100 nm and that virtually any chemical compound that is activated by light in this range and functions as a photosensitizing compound as discussed above and known to one of skill in this art may be used in the claimed method, and directs the skilled artisan to a comprehensive listing of photosensitive chemicals found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, (1989) (see paragraph [012]), the teachings of which are incorporated in their entirety by reference in the instant application (see paragraph [036]). The specification also includes specific teaching of the structure/function of indocyanine green, pyropheophorbide compounds and alkyl ether analogs of chlorins, and specifically incorporates by reference in their entirety the teachings of WO 92/00106 (Raven *et al.*); WO97/31582 (Abels *et al.*); Devisselle *et al.*, *SPIE* 2627:100-108 (1995); U.S. Patent No. 5,459,159; U.S. Patent No. 5,955,585; and U.S. Patent No. 5,952,366 (see paragraph [040]).

Further, the specification provides exemplary photosensitizing compounds, including any one or combination of chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD), porfimer sodium, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and pro-drugs such as δ-amino-levulinic acid, which can produce drugs such as protoporphyrin (see paragraph [036]), and pyropheophorbide compounds, bacteriochlorophyll derivatives, alkyl ether analogs of chlorins (see paragraph [040]).

Therefore, in light of the high level of skill in the art, the extensive teachings regarding photosensitizing compounds in the art, and the teachings of the specification, which provides at least 17 exemplars of photosensitizing compounds from various chemical classes, and which provides several working examples of photosensitizing compounds used in exemplary *in vivo* methods, it is respectfully submitted that it would not require undue experimentation for a skilled artisan to select a photosensitizing compound for use in the claimed methods.

c. Targeting Moiety

The Examiner alleges that, in order to make the conjugate for the claimed method, the targeting moiety such as the specific antigens, ligands, and receptors on the abnormal endothelium in the eye must first be identified; second, be made to bind specifically to the antigen, ligand or receptors; and third, linked to the particular photosensitizing compound for the claimed method. The Examiner alleges that until the specific antigen, ligand, receptor, binding pair and bispecific antibody comprising the specific ligand and receptor that binds to the abnormal endothelium in the eye have been identified, the specification merely extends an invitation to one skilled in the art to further experimentation to arrive at the claimed invention.

The Examiner also alleges that without guidance as to the structure of the photosensitizing compound and the binding specificity of the targeting moiety, it is unpredictable which undisclosed conjugate including the undisclosed photosensitizing compound conjugated to which undisclosed targeting moiety will target to abnormal endothelium in the eye. Further, it is alleged that there is insufficient *in vivo* working demonstrating that all undisclosed conjugate is effective to treat all neovascular disease of the eye. Applicant respectfully disagrees.

i. Identification of a Targeting Moiety

The Examiner alleges that the specification provides insufficient guidance as to the structure and function of the targeting moiety, such as a receptor, antigen, ligand or antibody, to which the targeted photosensitizing compound is conjugated. Applicant respectfully submits that the targeting moiety **is selected** to selectively bind to abnormal endothelium. Applicant respectfully submits that the exact structure of the targeting moiety is not relevant to patentability. For example, any receptor present on abnormal endothelium or ligand bindable to a receptor present on abnormal endothelium or antigen present on abnormal endothelium or antibody bindable to an antigen present on abnormal endothelium that is known in the art to selectively bind to abnormal endothelium is contemplated to be encompassed by the claimed method. The applicant respectfully submits that a patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). Receptors present on abnormal endothelium and ligands bindable to these receptors, and antigens present on abnormal endothelium and antibodies bindable to these antigens, were well known in the art at the time the application was originally filed. For example, Boulton *et al.* (Br. J Ophthalmol 82: 561-568 (1998)) discloses increased occurrence of VEGF levels and VEGF receptors in patients with diabetic retinopathy and using anti-VEGF antibodies for immunostaining. Prewett *et al.* (Cancer Research 59: 5209-5218 (1999) discloses Flk-1 as a surface receptor expressed on endothelial cells associated with tumor angiogenesis and using anti-Flk-1 antibodies in the treatment of angiogenesis-dependent tumors. Thorpe *et al.* (U.S. Patent 5,877,279) teaches that blood vessels of vascularized tumors present a number of surface-expressed components and cell surface receptors and antibodies directed thereto, including endoglin (TEC-4 and TEC-11 antibodies), a TGFβ receptor, E- and P-selectins, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE, an $\alpha_v\beta_3$ integrin, pleiotropin, endosialin, MHC Class II proteins and aminophospholipids.

Additional endothelial receptors known at the time the application was filed include, among others, the extra-domain B (ED-B) of fibronectin (Birchler *et al.*, *Nature Biotech.* 17:984 (1999)); endothelial-leukocyte adhesion molecule (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), the agent for leukocyte adhesion molecule-1 (LAM-1 agent), and HLA-DR,

HLA-DP or HLA-DQ (Thorpe, U.S. Patent No. 5,855,866 (1999); and the selectins, including L-Selectin (Rao *et al.*, U.S. Patent No. 5,624,909 (1997)).

The "function" of the targeting moiety is to allow selective binding or targeting of the photosensitizing compound to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens (see paragraphs [014] and [032]). The specification teaches a number of such targeting moieties, including a ligand bindable to a receptor present on abnormal endothelium and an antibody bindable to antigen present on abnormal (see paragraph [020]). The specification teaches that the targeting moiety can be one member of a binding pair. For example, the specification provides as specific examples of binding pairs a bindable fragment of the L19 antibody to the ED-B of fibronectin and the ED-B of fibronectin (paragraph [054]), VEGF and VEGF receptor (paragraphs [058] and [059]), integrin αvβ3 and anti-integrin αvβ3 antibody (paragraph [061]), and carcinoembryonic antigen (CEA) and anti-CEA antibody (paragraph [063]). Using binding pairs for targeting purposes was well known in this art at the time of the effective filing date of the claims (*e.g.*, see Thorpe *et al.* (U.S. Patent 5,877,279).

Thus, the specification teaches that a targeting moiety is selected to allow selective binding or targeting of the photosensitizing compound to abnormal endothelium that lines or composes neovascular target tissue in the eye. At the time of the effective filing date of the claims, there was extensive teachings in the art on targeting moieties, such as binding pairs, and on conjugating compounds to targeting moieties. The art made of record demonstrates that many targeting moieties that selectively bind to abnormal endothelium were known in the art at the time of the effective filing date of the claims.

Thus, the specification discloses generic and specific examples of targeting moieties for the conjugate of the claimed methods. The specification also provides working examples of exemplary targeting moieties conjugated to photosensitizing agents. Other targeting moieties, such as antigens, receptors or ligands that selectively bind to abnormal endothelium, are known in the art. Further, photosensitizing agents conjugated to targeting moieties were well known in the art at the time of the effective filing date of the claims. Hence, there is no need to include in the instant disclosure the "structure and function" of the targeting moiety in the

conjugate of the claimed methods. It is respectfully submitted that it would not require undue experimentation to select a targeting moiety to which a photosensitizing compound can be conjugated to provide specific targeting of the conjugate to abnormal endothelium.

ii. Antibody Binding Specificity

The Examiner alleges that, because the specific antigen, receptor or ligand is not disclosed in the specification, the binding specificity of the antibody is questionable, and alleges that the method is not enabled because without knowing the antibody binding specificity it is questionable whether the targeted photosensitizing compound would bind specifically to the undisclosed antigen on the abnormal endothelium. Applicant respectfully submits that none of the pending claims directed to any specific antibody. The pending claims are method claims. Claim 11 is directed to a method of treating neovascular disease of the eye that includes using a conjugate that includes a photosensitizer compound conjugated to one member of a binding pair, where the binding pair is selected, in one embodiment, to include an antibody bindable to endothelial receptors and/or antigens. Thus, the overall structure of the antibody and its exact binding specificity is not pertinent to patentability. The antibody is selected to have the ability to combine specifically or with a high degree of affinity for abnormal endothelium when compared to its reactivity toward non-target tissue, so that the antibody can serve as a targeting moiety by which a photosensitizing compound conjugated to the antibody can selectively bind to abnormal endothelium.

The specification teaches that the antibody is **selected** to be bindable to endothelial receptors and antigens ([014]), and provides as examples antibody elicited to an antigenic determinant on abnormal endothelium, such as the extra domain B of fibronectin (paragraph [021]) and αvβ3 integrins (paragraph [061]) or to antigen associated with choroidal tumor, such as carcinoembryonic antigen (paragraph [063]). Methods of making antibodies with specificity to abnormal endothelium were known at the time the application was originally filed (see Thorpe, U.S. Patent No. 5,855,866 (issued January 5, 1999)).

Thus, antibodies bindable to abnormal endothelium and methods of making such antibodies were known at the time of the effective filing date of the claims. Hence, it is not necessary to include this disclosure in the instant specification. Notwithstanding this, the specification includes generic and specific examples of

antibodies having specificity to abnormal endothelium, and provides working examples of exemplary antibodies. One skilled in the art can select an antibody from any of the known antibodies bindable to abnormal endothelium, as disclosed in the art or in the instant specification, to serve as a targeting moiety in the conjugate of the methods claimed herein. Thus, applicant respectfully submits that the skilled artisan would be able to select an antibody having specificity to abnormal endothelium to allow targeting of the photosensitizing compound to abnormal endothelium without undue experimentation.

d. *In Vivo* Demonstration of Effectiveness

The Examiner alleges that there is insufficient *in vivo* working examples demonstrating that all "undisclosed conjugates" are effective to treat all neovascular disease of the eye. Applicant respectfully submits that neovascular diseases of the eye share a common underlying etiology, as discussed in more detail below. In addition, as discussed below, photosensitizing agents share certain characteristics. Further, Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for an area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, method; rather, even in an unpredictable art, a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill in the art how to make and use the claimed subject matter without undue experimentation.

1. Neovascular Diseases of the Eye Share a Common Underlying Etiology

Applicant respectfully submits that neovascular diseases of the eye share a common underlying pathology, and thus agents effective against the underlying pathology are effective against such disorders generally. These disorders involve proliferation of endothelial cells, and the conjugates target such cells.

With due respect to the Examiner, one of skill in the art at the time of application would have known that neovascular diseases share as an underlying etiology uncontrolled angiogenesis (for example, see D'Amato, US 5,712,291 (1998)). Angiogenesis involves the generation of new blood vessels

(neovascularization) in a tissue or organ. Neovascularization involves recruitment and proliferation of endothelial cells. Hence targeting endothelial cells targets neovascularization and the consequences thereof.

D'Amato discloses that under normal physiological conditions, humans or animals only undergo angiogenesis in specific restricted situations, such as in wound healing and fetal and embryonal development. D'Amato also discloses that the control of angiogenesis is a highly regulated system of angiogenic stimulators and inhibitors and that the control of angiogenesis has been found to be altered in certain disease states and, in many cases, the pathological damage associated with the disease is related to the uncontrolled angiogenesis.

D'Amato discloses that persistent, unregulated angiogenesis occurs in a multiplicity of disease states. D'Amato also discloses that one example of a disease mediated by angiogenesis is ocular neovascular disease, which is characterized by invasion of new blood vessels into the structures of the eye such as the retina or cornea. It is the most common cause of blindness and is involved in approximately twenty eye diseases. In age-related macular degeneration, the associated visual problems are caused by an ingrowth of chorioidal capillaries through defects in Bruch's membrane with proliferation of fibrovascular tissue beneath the retinal pigment epithelium. Angiogenic damage is also associated with diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrolental fibroplasia. These processes require recruitment and proliferation of endothelial cells and endothelium. Other diseases associated with corneal neovascularization include epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium, keratitis, sjogrens syndrome, phylectenulosis, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, polyarteritis nodosa, trauma, Wegeners sarcoidosis, scleritis, Steven's Johnson disease, periphigoid radial keratotomy, and corneal graph rejection (see D'Amato).

Diseases associated with retinal/choroidal neovascularization include diabetic retinopathy, macular degeneration, sickle cell anemia, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales disease, Bechets disease, infections causing a

retinitis or choroiditis, presumed ocular histoplasmosis, Bests disease, optic pits, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications. Other diseases include diseases associated with rubeosis and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy (see D'Amato). Hence, the pathological damage associated with the disease is related to the uncontrolled angiogenesis, and therefore neovascular diseases of the eye share as a common underlying pathology and etiology excessive recruitment and proliferation of endothelial cells. Hence targeting endothelial cells targets neovascularization and the consequences thereof.

2. PDT For Treatment of Neovascularization

The instant claims are directed to methods of photodynamic therapy (PDT) to treat neovascular diseases of the eye by targeting proliferating endothelial cells and tissues (abnormal endothelium that lines or composes neovascular tissue). As disclosed in the specification and known the those skilled in the art at the effective filing date of the claims at issue, PDT is a treatment that is based on photochemical reactions induced by exposure of the photosensitizing compound to light of an appropriate wavelength. The light causes the photosensitizing compound to generate chemically disruptive species that disrupts or destroys the cell through reaction with cellular components or nuclear membranes (Weinstein et al., U.S. 4,753,958, col. 3, lines 9-38). Photosensitizing compounds are preferentially absorbed and selectively retained by hyperproliferative cells compared to normal cells. The preferential uptake and accumulation of the photosensitizing agent by hyperproliferating cells generally limits the destructive effects of PDT to these cells. In prior art methods, the cytotoxicity is not exclusive to hyperproliferating cells, and PDT can damage or destroy "healthy" cells that uptake the photosensitizer, resulting in erythema, edema, ulceration, and necrosis (Spikes, Annal. N. Y. Acad. Sci., page 497, second full paragraph). The instant specification, however, teaches that these peripheral reactions can be minimized by administering the photosensitizing compound as a conjugate that includes a targeting moiety that selectively targets a specific tissue, such as hyperproliferative cells of neovascular tissue and by selection and titration of the administered light and time for administration.

3. Photosensitizing Agents Share Certain Characteristics

The specification and the art at the time of the effective filing date of claims at issue, teach that photosensitizing compounds share a number of characteristics. For example, a photosensitizing compound is preferentially taken up and selectively retained by hyperproliferative cells compared to normal cells (Kessel *et al.*, *Photochem Photobiology* 58(2):200-203 (1993), page 200, first paragraph; Dougherty, *Seminars in Surgical Oncology* 2:24-37 (1986), page 24, first paragraph; and Pandey *et al.*, *J Molecular Recognition* 9: 118-122 (1996), page 118, first paragraph). Subsequent irradiation of the photosensitizing compound causes a photochemical reaction that is believed to generate chemically disruptive species, such as singlet oxygen, which disrupt or destroy the cell through reaction with cellular components or nuclear membranes (Weinstein et al., U.S. Patent 4,753,958, col. 3, lines 9-38). Preferably, the chemical compound is nontoxic to the subject to which it is administered or is capable of being formulated in a nontoxic composition and the chemical compound in its photodegraded form also is nontoxic (see, e.g. paragraph [036] of the instant application). The specification directs the skilled artisan to a comprehensive listing of photosensitive chemicals may be found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, 1989 (see, e.g. paragraph [036]). A certain amount of experimentation is permissible as long as it is not undue. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. Applicant respectfully submits that routine testing can be used to determine whether a compound generates chemically disruptive species upon exposure to light in the range of 500nm-1100nm, for example, or to determine whether it is toxic or non-toxic in its native and photodegraded state. Thus, the amount of experimentation required to determine whether a photosensitizing compound can be used in the methods as instantly claimed is not undue. Furthermore, a wide variety of such compounds were known to those of skill in the art at the time of the effective filing date of the application.

4. Examples in the Specification

The specification provides several working examples illustrating various photosensitizing compounds in the claimed methods for treating neovascular disease of the eye. Specifically, EXAMPLE 1 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound verteporfin conjugated to

a bindable fragment of the L19 antibody demonstrating high affinity to the ED-B of fibronectin in a method to treat choroidal neovasculature lesions (see paragraphs [053] - [057]). EXAMPLE 2 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound a benzoporphyrin derivative conjugated to VEGF in a method to treat retinal neovasculature lesions (see paragraphs [058] through [060]). EXAMPLE 3 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound texaphyrin conjugated to antibody elicited to αvβ3 in a method to treat vascular tumors of the eye (see paragraphs [061] and [062]). EXAMPLE 4 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound both texaphyrin conjugated to antibody elicited to αvβ3 and a benzoporphyrin derivative conjugated to an antibody elicited to carcinoembryonic antigen in a method to treat choroidal tumors of the eye (see paragraphs [063] through [066]).

Thus, the specification provides working examples that demonstrate that various photosensitizing agents are used in a conjugate in the claimed methods. As discussed above, photosensitizing compounds were well known in the art at the time of filing the original application. In addition, receptors present on abnormal endothelium, ligands bindable to a receptor present on abnormal endothelium, antigens present on abnormal endothelium or antibodies bindable to an antigen present on abnormal endothelium were well known in the art at the time of the effective filing date of the claims. There is no reason provided to doubt that photosensitizing compounds other than the exemplary photosensitizing compounds provided in the examples when conjugated to a targeting agent that targets abnormal endothelium will not be effective. Effectiveness is demonstrated in the specification for conjugates including verteporfin conjugated to a bindable fragment of the L19 antibody demonstrating high affinity to the ED-B of fibronectin, a benzoporphyrin derivative conjugated to VEGF, texaphyrin conjugated to antibody elicited to αvβ3 and a benzoporphyrin derivative conjugated to an antibody elicited to carcinoembryonic antigen.

As is known to those of skill in the art, the level of knowledge and skill in the construction and assay of conjugates of photosensitizing compounds and targeting moieties was so high as of the effective filing date that it would not have required undue experimentation by one of skill in the art to substitute either a different

photosensitizing compound or a different targeting moiety for the exemplified components of the conjugates of the instant application such that the resulting therapeutic agent is effective for treating neovascular disease of the eye. Further, it would not have required undue experimentation to assay conjugates wherein such substitutions have been made. The specification also teaches how to evaluate the effectiveness of the method in treating neovascular disease of the eye, such as standard visual acuity testing, ophthalmoscopy, color fundus photography and stereo fluorescein angiography (see paragraphs [053] and [057]).

Thus, in light of the extensive teachings and examples in the specification, the high level of skill of those in this art, and the knowledge of those of skill in the art, applicant respectfully submits that it would not require undue experimentation for the skilled artisan to make and use conjugates to be used in the claimed methods that have either a photosensitizing compound or a targeting moiety different from those disclosed in the Examples as exemplary components of the conjugate.

Therefore, because neovascular diseases of the eye share as an underlying pathology excessive cell proliferation caused by unregulated or abnormal angiogenesis, and the specification provides guidance as to how to make and use conjugates of photosensitizing compounds and targeting moieties to selectively delivery a photosensitizing compound to such neovascular tissue, and the specification provides working examples of such compounds, and assays to test the effectiveness of such conjugates, a conjugate including a photosensitizing agent and a targeting moiety that demonstrates preferential association with abnormal endothelium of neovascular tissue is effective generally in treating neovascular disease of the eye.

e. Step of Illumination

The specification teaches that the duration of illumination will be determined empirically. As an example, the specification describes a total or cumulative period of time between 4 minutes and 148 hours (for example, see paragraph [048]). The specification also teaches that the total fluence of the light is between 30 Joules and about 25,000 Joules (for example, see paragraph [049]) using an intensity of light substantially less that 500 mW/cm^2, where a combination of an intensity of light used for illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue

through which the light passes remains undamaged (see paragraph [[050]). Thus, an upper limit of illumination and time of exposure are that selected so that no damage to non-target tissue occurs.

The instant application recognizes the need for a method of photodynamic therapy that reduces the risk of damage to non-target tissues and yet can be used to effectively treat target tissues such as neovascular disease of the eye. The instant application teaches the significance and applicability of the alteration of two particular treatment parameters, i.e., the intensity of light and the duration of irradiation, in combination with the use of a targeted photoreactive compound in achieving the needed method without limiting the number and types of photoreactive compounds or the type of targeting moieties that can be used in the method. As described in the instant application, these parameters are selected to provide for a relatively high total fluence of radiation that is sufficiently high to activate the photosensitizing agent. The optimal total fluence can be determined empirically, for example, in a light dose escalation trial. The high total fluence is administered in such a way that minimal to no collateral damage is incurred by non-target or normal tissue. For example, the total fluence can be achieved by administering light at a relatively low fluence rate or intensity for a prolonged period of time. The duration must be sufficient to photoactivate enough photosensitizing compound to achieve the desired effect on the target site. Thus, the instant application teaches the types of alterations of the parameters of radiation administration that can be used to achieve activation of targeted photosensitive compounds in target tissues for destruction of target tissues, and in particular, abnormal endothelium in neovascular diseases, without collateral damage to non-target tissues.

i. Alleged Lack of Upper Limit of Illumination

The Examiner alleges that even if the photosensitizing compound is enabled, the light source, the combination of the intensity of light used for the step of illumination and the duration of illumination to arrive at the total fluence "are critical for the claimed method" and that "given the lack of an upper limit for the duration of illumination, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues." Applicant respectfully disagrees. The specification teaches at paragraphs [013] - [016] that:

> The present invention describes methods to treat neovascular disease of the eye based on the precise targeting of photosensitive compounds to target tissue and the activation of these targeted photosensitizer compounds by subsequently administering to the subject non-coherent (non-laser) or coherent (laser) light of a relatively low fluence rate over a prolonged period of time.
>
> The present invention further discloses the selective binding of the photosensitizing agent to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens. This targeting scheme decreases the amount of sensitizing drug required for effective therapy, which in turn reduces the fluence rate or light irradiation needed for effective photoactivation. As a result, the disclosed method achieves maximal dosage to abnormal endothelium with minimal side effects or collateral tissue damage.
>
> Additionally, the present disclosure teaches the unexpected use of a low power non-coherent light source utilized for longer than about 4 minutes. This teaches away from the use of a high powered, brief exposure using laser light, results in fuller, more efficient activation of the bound photosensitizers, and enables a high therapeutic index using a low dose drug. Moreover, a low power non-coherent light source is relatively inexpensive and simpler to use. Finally, because the present invention teaches photoactivation with a non-coherent, broadband light source, different types of photosensitizers can be activated with a single light source.
>
> Due to the highly specific nature of the photosensitizer uptake, excess light or light falling on nonpathologic areas causes no unwanted photoactivation. Therefore, a region of the retina or macular with diffuse abnormalities can be safely treated without damaging intervening normal eye structures. In addition, eye movement by the patient during treatment, which can result in the further exposure to light of normal eye structures, is harmless. Thus, the use of highly targeted photosensitizers allows the delivery of light in a diffuse fashion and over a prolonged illumination period. In fact, one embodiment of the invention is the use of ambient light to activate the photosensitized neovascular tissue.

Thus, the specification discloses that selection of a combination of a low intensity light and a prolonged duration of irradiation to activate the photosensitizer reduces the potential for damage to non-target tissue exposed to the irradiation. Contrary to the Examiner's assertion, there is no "lack of an upper limit for the duration of illumination." An upper limit is disclosed as being selected so that no damage to non-target tissue occurs. Thus, a functional upper limit exists. The specification teaches, at paragraph [050], that the duration of illumination depends on the intensity of the light chosen so that the desired total fluence is achieved:

> The intensity or power of the light used is measured in watts, with each Joule equal to one watt-sec. Therefore, the intensity of the light used for irradiating in the present invention may be substantially less than 500 mW/cm^2. Since the total fluence or amount of energy of the light in Joules is divided by the duration of total exposure time in seconds, the longer the amount of time the target is exposed to the irradiation, the greater the amount of total energy or fluence may be used without increasing the amount of the intensity of the light used. The present invention employs an amount of total fluence of irradiation that is sufficiently high to activate the photosensitizing agent, as applicable, with a concomitant reduction in the intensity of light and collateral or non-target specific tissue damage.

Thus, a total fluence of light sufficient to photoactivate the photosensitizing compound to achieve the desired effect at a target site can be achieved by a combination of extended duration of irradiation and a concomitant reduction in the intensity of the light used. The specification teaches (paragraphs [013] and [014] that the disclosed targeting scheme decreases the amount of sensitizing drug required for effective therapy, which in turn reduces the fluence rate or light irradiation needed for effective photoactivation, and that a combination of a relatively low fluence rate of light over a prolonged period of time results in a method that achieves maximal dosage to abnormal endothelium with minimal side effects or collateral tissue damage. The specification provides exemplary combinations of the duration of irradiation and light intensity. For example, the specification teaches irradiating a subject in one or more sessions for a total period of 10 minutes with 400 mW/cm^2 of light to produce a total fluence of 240 Joules/cm^2 (see paragraph [055]); irradiating a subject with 500 mW/cm^2 of light for a period of approximately 20 minutes in one or more sessions to produce a total fluence of illumination of about 600 Joules/cm^2 (see paragraph [059]); and irradiating a subject with 250 mW/cm^2 of light for about 1 hour over the course of one or more sessions to provide a total fluence of 900 J/cm^2. Hence, one skilled in this art, in light of the teachings of the specification, and that which is known in the art at the time of the effective filing date of the claims, would be able to select a combination of light intensity and a duration of irradiation to activate the photosensitizer while minimizing any damage to non-target tissue.

2. Evaluation of the other *In re Wands* Factors

Applicant incorporates by reference herein the discussion of the *In re Wands* factors in the previous response.

a. Scope of the claims

The Examiner states (Office Action, page 8, last paragraph) that the scope of the claims encompasses a method to treat all neovascular disease of the eye that includes administering [any] conjugate including any photosensitizing compound conjugated to any targeting moiety that selectively binds to abnormal endothelium that lines or composes target tissue of the eye. Applicant agrees with this assessment of the scope of the claims. As discussed above, neovascular diseases of the eye share a common underlying pathology – excessive recruitment and proliferation of endothelial cells caused by abnormal angiogenesis.

The instant specification teaches using photodynamic therapy methods to treat such neovascular diseases. The specification discloses how to make and use conjugates of photosensitizing compounds and targeting moieties to selectively deliver a photosensitizing compound to endothelial cells. Targeting endothelial cells targets abnormal neovascularization and the consequences thereof. The specification provides working examples of such conjugates and assays to test the effectiveness of such conjugates. D'Amato (US 5,712,291) discloses that many neovascular diseases of the eye, including those associated with corneal neovascularization, retinal/choroidal neovascularization and the abnormal proliferation of fibrovascular tissue, share as an underlying etiology an uncontrolled angiogenesis or excessive recruitment and proliferation of endothelial cells. The instant claims are directed to methods effective against the underlying pathology, and thus are effective against such neovascular diseases generally. Thus, the instant claims, which are directed to PDT methods including a conjugate having a photosensitizing agent and a targeting moiety that demonstrates preferential association with abnormal endothelium of neovascular tissue, are effective generally in treating neovascular disease of the eye.

b. Level of Skill in the Art

The level of skill in the art is high, as evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees. The art is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. In fact, the prior art indicates that studies in the 1970s and 1980s were directed to using porphyrins

and chlorins for treatment of hyperproliferative and neoplastic vascular tissue (Williams *et al.* (U.S. 5,576,013; 1996). The age of the cited art is a strong factor supporting the view that the skilled artisan would have been familiar generally with use of photosensitizing compounds in photodynamic therapy. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

c. State of the Art

At the time of the effective filing date of the claims, a broad body of knowledge had amassed in the areas of pharmaceutical sciences, medicine, and biochemistry directed to the use of photodynamic therapy as a treatment for hyperproliferative tissues such as neovascularization. Many of these articles and patents have been made of record in this application. Many photosensitizing compounds were known to those skilled in this art at the time the application was originally filed, including hematoporphyrins, porphyrins, chlorins, bacteriochlorins, benzoporphyrins, phthalocyanines, metallo-phthalocyanines and purpurines and their derivatives; naphthalocyanines, texaphyrins, porphycenes, platyrins and other extended tetrapyrroles (Kreimer-Birnbaum, *Sem Hematol. 26(2)*: 157-173 (1989)). Richter *et al.* (U.S. Patent No. 5,770,619) discloses photosensitizing compounds including merocyanines, pheophorbides, psoralens, monoaspartyl chlorin, zinc phthalocyanine, tin etiopurpurin and porfimer sodium, and pro-drugs such as δ-aminolevulinic acid which can produce drugs such as proto-porphyrin in tissue. Other known PDT agents include indocyanine green, zinc phthalocyanine, rose bengal, epigallocatechin, epicatechin derivatives, hypocrellin B, urocanic acid, indoleacrylic acid, rhodium complexes, etiobenzochlorins, octaethyl-benzochlorin, sulfonated Pc-naphthalocyanine, chloroaluminum sulfonated phthalocyanine, Merocyanin 540, Hoechst 33258, acridine compounds, suprofen, tiaprofenic acid, furocoumarin hydroperoxides, Victoria blue BO, methylene blue and toluidine blue (U.S. Patent No. 5,576,013 (Williams *et al.*, 1996)). Kessel *et al.* (*Photochemistry and Photobiology 58(2)*: 200-203 (1993) discloses assays useful as predictive of the efficiency of photosensitizing compounds in PDT. Henderson *et al.* (Cancer Research 57: 4000-4007 (1997) teaches that tumor cell photosensitization, tumor response and vascular photosensitization are linked through common mechanisms.

These references to numerous published protocols for PDT, for identifying, producing and/or extracting photosensitizing compounds, and using such

compounds to treat a variety of hyperproliferative tissues, including neovascular tissue, demonstrate the large volume of information regarding tested and reliable procedures available at the time of the effective filing date of the claims, and thus evidence the state of the art at the relevant time.

CONCLUSION

In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, and the knowledge of those of skill in this art, it would not require undue experimentation for a person of skill in the art to select a targeting moiety and a photosensitizing compound to practice a method of photodynamic therapy to treat neovascular disease of the eye as claimed; or to select as a targeting moiety one member of a binding pair that includes an antibody, an antigen, a ligand, or a receptor specific for abnormal endothelium to practice a method of photodynamic therapy to treat neovascular disease of the eye as claimed. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter of claims 1-6, 11, 12, 16-24, 36 and 38-49. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Exemplified Steps Are Enabled

Applicant notes that the Examiner states that the exemplified steps are enabled in the specification. The mere fact that the precise steps of the embodiment exemplified in the specification are not recited in the claims does not provide sufficient reason to hold the claims non-enabled. The enablement requirement of 112, first paragraph, does not require that the claims recite specific elements for "photosensitizing compound" or "binding pair" or "endothelial antigen or ligand" or a specific "targeting moiety" or even that the specification recite specific elements for all circumstances, when such elements can be readily determined by one skilled in the art using the teachings of the specification. As discussed, various "photosensitizing compounds" and "binding pairs" and "endothelial antigens" and "endothelial ligands" and "targeting moieties that selectively bind to abnormal endothelium" are known in the art. Reciting precise elements in the claims would be unduly limiting and should not be required.

In this instance, applicant is providing a general method of photodynamic therapy to treat neovascular disease of the eye. To limit the claims to specific elements for "photosensitizing compound" or "binding pair" or "endothelial antigen" or "endothelial ligand" or a specific "targeting moiety that selectively binds to abnormal endothelium" would permit those of skill in the art to practice the claimed method, but avoid infringement, merely by substituting different elements to achieve the same outcome, which are known or could be readily identified using the methods described in the specification and known in the art.

REBUTTAL TO EXAMINER'S ARGUMENTS

1. Klyashchitsky *et al.*

The Examiner alleges that Klyashchitsky *et al.* teaches "that the property of photosensitizing compound is a very important factor determining the choice of photosensitizing compound to be used as well as the selectivity of photosensitizing compound" (see Office Action page 5). Applicant respectfully submits that the cited section of Klyashchitsky *et al.* does not discuss the **structure** of a photosensitizing compound as a very important factor in selecting a photosensitizing compound. The reference states on page 1, column 1, that:

> Photodynamic therapy is a new approach to cancer treatment[1]. It is based on two properties of hematoporphyrin (HP) derivatives and related macrocycles: (1) preferential tumor tissue localization and (2) the ability to generate $^1O_2$ subsequent to light activation [2]. The above properties finally promote the photodynamic cell killing. The reasons for the partially selective PS [photosensitizer] accumulation in tumors are not yet totally understood. This property is a very important factor determining the choice of PS to be used, effective PS and light doses, as well as the optimal protocol of clinical treatment and minimization or elimination of harmful side effects of PDT.

Thus, the "property" referred to by Klyashchitsky *et al.* in the section cited by the Examiner refers to the partially selective accumulation of photosensitizer compounds in tumors. There is no mention of "structure" in the cited section. Klyashchitsky *et al.* teaches that the selective accumulation of photosensitizer compounds in tumors can be improved by conjugating the photosensitizing compound to targeting compounds, such as antibodies, lectins and hormones (see abstract and whole document). The pending claims are directed to methods to treat neovascular disease that include administering a photosensitizing compound conjugated to a targeting moiety.

Hence, the conjugates used in the claimed methods do not depend on the "partially selective accumulation of photosensitizer compounds" property of Klyashchitsky *et al.* because the conjugates in the instant methods are specifically targeted to abnormal endothelium that lines or composes neovascular tissue in the eye by the use of a targeting moiety. It is respectfully submitted that such a selective reading of Klyashchitsky *et al.*, in which statements regarding factors important in selecting a photosensitizer compound are taken out of context, has resulted in a mischaracterization of the reference that cannot validly be relied upon to support an allegation that the structure of a photosensitizing compound is a very important factor determining the choice of photosensitizing compound.

Finally, Klyashchitsky *et al.*, which published in 1994, is not particularly pertinent for establishing the state of the art at the time of filing of the claims at issue. The instant application was filed in January 2001 and ultimately priority to an application filed in January 2000. A 1994 article is not representative of the state of the art in 2000.

2. Protein Structure

The Examiner alleges that without the guidance as to the protein structure of the antigen, the receptor, or the ligand, it is allegedly unpredictable which undisclosed antigen, receptor and ligand would be effective for targeting any photosensitizing compound to abnormal endothelium. Applicant respectfully disagrees. First, none of the pending claims claim as subject matter a specific antigen, receptor, or ligand. Instead, the claims are directed to a method of treating neovascular diseases of the eye using a conjugate that includes a photosensitizing compound conjugated to a targeting moiety, such as an antigen, receptor or ligand that selectively associates with abnormal endothelium. Hence the conjugates used in the methods target receptors and/or antigens on endothelial cells. The receptors on proliferating endothelium are well known, as are ligands or antigens or other molecules that specifically bind thereto (see discussion above). Also, the overall structure of an antigen, receptor or ligand is not relevant to patentability, since such moieties are well known.

Second, one skilled in the art can **select** any antigen, receptor or ligand known to selectively associate with abnormal endothelium as a targeting moiety in the claimed method. As discussed above, the literature discloses and one skilled in

this art is familiar with a number or different antigens, receptors and ligands associated with abnormal endothelium. Further, the applicant submits that the claimed antigens, receptors or ligands are not restricted to being a protein. It is well known to those skilled in this art that antigens and ligands are not limited to proteins, but include carbohydrates, such as the blood group antigens (see Janeway *et al.*, Immunobiology, 3rd ed., 1997, page 2.12), glycans, lipopolysaccharides or peptides (Janeway *et al.*, pages 3:8, 3:9 and 9:11).

REJECTION OF CLAIMS 1-6, 11, 12, 16-24, 36, 42 AND 46-49 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - Written Description

Claims 1-6, 11, 12, 16-24, 36, 42 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner contends that there is insufficient written description of (1) the structure and function of the photosensitizing compounds "benzoporphyrin derivative," "bacteriochlorophyll derivative" or "ether analogs"; (2) the genus of conjugate to be used in the claimed methods because no description of the structural features of the photosensitizing compound and the structural features of the targeting moiety used in the conjugate that are common to the genus are provided; (3) the binding specificity of any antibody, or the targeted antigen; and (4) the duration of illumination and intensity of light and thus the Examiner alleges it is unclear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The Examiner also alleges that the method step of allowing non-specifically bound photosensitizing compound to clear from collateral tissues is missing in the claims.

This rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] *Vas-Cath, Inc. v. Mahurkar*, at 1115, quoting *In re Ruschig*, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

THE CLAIMS

The claims are discussed above.

ANALYSIS

1. The Structure and Function of the Photosensitizing Compounds

The Examiner alleges that there is inadequate written description about the structure of conjugates including "benzoporphyrin derivative," "bacteriochlorophyll derivative" or "ether analogs." Applicant respectfully disagrees. The structure and function of photosensitizing compounds were well known at the time of the effective filing date of the claims at issue.

a. Benzoporphyrin derivatives

As discussed above, at the time of filing of this application and the parent application, benzoporphyrin derivatives were known to those of skill in the art (for example, see Liu, U.S. Pat. No. 5,053,423; Chang *et al.*, U.S. Pat. No. 5,064,952; Gulliya *et al.*, U.S. Pat. No. 5,091,385; and Allision *et al.*, U.S. Pat. No. 5,214,036). The methodology for preparing benzoporphyrin derivatives also was known in the art at the time of filing the original application (for example, see Gulliya *et al.*, U.S. Pat. No. 5,091,385 and Pangka *et al.*, J. Org. Chem. 51:1094-1100 (1986). A. M. Richter *et al.* ("Benzoporphyrin and Benzoporphyrin Derivatives (BPDs)," J. Natl. Cancer Inst. 79:1327-32 (1987)) discloses preliminary studies on the phototoxicity of BPDs (see also A. M. Richter *et al.*, Proceedings of SPIE--The International Society for Optical Engineering, 997:132-38 (1988)). Kessel (Photochem. Photobiol. 49:579-82 (1989)) examined *in vitro* photosensitization with a BPD.

As demonstrated by the references cited here as well as others in this art and those already made of record, benzoporphyrin derivatives, their structures and methods of making them were well known in the art at the time of the effective filing date of the claims. The applicant respectfully submits that a patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

Further, methods of conjugating benzoporphyrin derivatives to ligands reactive with a target were known in the art. For example, Richter *et al.* (U.S. Patent No. 5,945,439 (1999)) teaches conjugating benzoporphyrin derivatives to specific ligands reactive with a target, such as receptor-specific ligands. It is further submitted that conjugating binding pairs to photosensitizing compounds was also known to those of skill in the art at the time the application was filed (for example, see Fritzberg *et al.*, U.S. 5,976,535 (1999); Davalian *et al.*, U.S. 5,616,719 (1997); and Pease *et al.*, U.S. 5,618,732 (1997)).

Applicant respectfully submits that the written description requirement may be met by an express disclosure. The specification expressly discloses conjugates that include benzoporphyrin derivatives as the photosensitizing compound (for example, see paragraphs [036], [058] and [063]). Thus, one skilled in the art would recognize that the applicant had possession of the claimed subject matter at the time of the effective filing date of the claims.

b. Bacteriochlorophyll Derivative

The applicant respectfully submits that the instant specification expressly discloses bacteriochlorophyll derivatives as the photosensitizer compound of the contemplated conjugates (for example, see paragraph [040]). Use of bacterio-chlorophyll derivatives as photosensitizer compounds was well known in this art at the time of the effective filing date of the claims. For example, at page 11, paragraph [040], the specification directs those skilled in the art to Scherz *et al.* (U.S. Pat. No. 5,955,585 (1999), entitled "Catalytic condensation method for the preparation of chlorophyll and bacteriochlorophyll derivatives"). Thus, one skilled in the art would recognize that the patent applicant had possession of the claimed subject matter at the time of filing of the original application. Applicant notes that Scherz *et al.* is incorporated by reference in its entirety in the instant application. If necessary, applicant can directly incorporate the teachings of Scherz *et al.* into the specification.

c. Ether analogs

As discussed above, applicant respectfully submits that the claimed subject matter includes embodiments where the photosensitizer compounds in the conjugates are "alkyl ether analogs of chlorins" (see, for example, claim 42). The applicant respectfully submits that the instant specification expressly discloses alkyl ether analogs of chlorins as the photosensitizer compound of the contemplated conjugates (for example, see paragraph [040]). Alkyl ether analogs of chlorins were well known in the art at the time of the effective filing date of the claims, and the application directs the skilled artisan to exemplary art. For example, at page 11, paragraph [040], the specification directs those skilled in the art to Pandey *et al.* (U.S. Pat. No. 5,952,366 (1999), entitled "Alkyl ether analogs of chlorins having an N-substituted imide ring"). Pandey *et al.* teaches the structures of the alkyl ether analogs of chlorins and methods for preparing the compounds. Applicant notes that Pandey *et al.* is incorporated by reference in its entirety in the instant application. If necessary, applicant can directly incorporate the entire teachings of Pandey *et al.* into the instant specification.

Further, methods of conjugating chlorins to targeting moieties to specifically target the photosensitizing compound were known in the art. For example, Rakestraw *et al.* teaches conjugating a chlorin via covalent bonds to monoclonal antibodies (Rakestraw *et al.*, *Proc. Nat. Acad. Sci. USA 87*: 4217-4221 (1990). Sternberg *et al.* (*Tetrahedron 54*: 4151-4202 (1998)) teaches conjugating porphyrins to biomolecules including antibodies, steroids, sugars, and polynucleotides. Fritzberg *et al.* (U.S. 5,976,535 (1999)) teaches conjugating cytotoxic agents to one member of a ligand/anti-ligand binding pair, and teaches conjugation to a receptor, an oligonucleotide, an enzymatic substrate or other binding site present on or in the target cell population.

Thus, applicant respectfully submits that the specification expressly discloses alkyl ether analogs of chlorins as the photosensitizer compound of the contemplated conjugates. One of skill in the art would recognize that the applicant had possession of the claimed subject matter at the time of filing of the original application. Applicant requests that the rejection be reconsidered and withdrawn.

2. Alleged Inadequate Description of the Claimed "Genus of Conjugate"

The Examiner alleges that neither the exemplary embodiments nor the specification's general method describes the structural features of the

photosensitizing compound and the structural features of the targeting moiety within the conjugate that are common to the genus. The Examiner further alleges that the disclosed species do not appear to be a representative number of species within the genus for the claimed methods. The Examiner states that "in essence, the specification simply directs those skilled in the art to go figure out for themselves what the conjugate in the claimed method look [*sic*] like" (see Office Action page 17). Applicant respectfully disagrees.

Applicant respectfully submits that applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied. The analysis for compliance with the written description requirement where claims are directed to a genus is as follows:

a) does the art indicate substantial variation among the species within the genus?; and

b) are there a representative number of examples explicitly or implicitly disclosed in the application as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species?

a. The "Claimed Genus"

Claim 1 is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes administering a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovasculature tissue. It appears from the Office Action that the Examiner considers "the conjugate" of the claimed method to be a "genus." The conjugate includes a "photosensitizing compound" (which represents a genus) and a "targeting moiety" (which represents a genus). The "conjugate genus" encompasses the exemplified species and other species that are similar in function to the exemplified species.

b. Structural Features

The Examiner alleges that the specification does not adequately describe the "conjugate genus" to be used in the methods because the specification fails to describe the structural features of the photosensitizing compound and the structural features of the targeting moiety that are common to the genus. Applicant is not aware

of any requirement under current U.S. patent law requiring disclosure of the **structural** similarities, if any, that are common the members of a given genus in order to fulfill the written description requirement under 35 U.S.C. § 112. The analysis for compliance with the written description requirement where claims are directed to a genus includes assessing whether the skilled artisan would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species.

i. Photosensitizing compounds

Those skilled in the art recognize that photosensitizing agents as a category share properties that make them effective in photodynamic therapy, among which are preferential tumor tissue localization and the ability to generate $^1O_2$ subsequent to light activation (for example, see Klyashchitsky *et al.*, first paragraph) or other cytotoxic materials such as superoxide, hydroperoxyl or hydroxyl radicals (see Sessler *et al.*, US 5,252,720 (1993)). Hence, the only "structural" requirement of photosensitizing compounds is that they be capable of generating cytotoxic materials upon exposure of the compound to light corresponding at least in part with the characteristic light absorption waveband of the photosensitizing compound in the presence of oxygen. It is respectfully submitted that no evidence is provided to support the Examiner's position that photosensitizing compounds as a genus share any specific structural features in common. The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well- known" in the art. *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The facts of which the Examiner is taking notice are conclusory and are not capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. *In re Malcolm*, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

Hence, if this position is maintained, the Examiner must provide a reference supporting this position. As discussed above, the Examiner's citation of Klyashchitsky *et al.* as support for the proposition that "structure" is an important factor in determining the choice of photosensitizing compound to be used is without merit. The cited section of Klyashchitsky *et al.* does not discuss the **structure** of a photosensitizing compound. The "property" referred to by Klyashchitsky *et al.* in the section cited by the Examiner refers to the partially selective accumulation of photosensitizer compounds in tumors. The selective reading of Klyashchitsky *et al.*, in which statements regarding factors important in selecting a photosensitizer compound are taken out of context, has resulted in a mischaracterization of the reference that cannot validly be relied upon to support an allegation that the structure of a photosensitizing compound is a very important factor determining the choice of photosensitizing compound.

The instant claims are directed to methods of photodynamic therapy to treat neovascular disease of the eye that include administering a targeted photosensitizing compound, such as a conjugate that includes a photosensitizing agent conjugated to a targeting moiety. The instant specification teaches that the photosensitizing compounds possess common elements or attributes. For example, the instant application teaches that, when a photosensitizing compound is contacted by radiation, it absorbs light, which results in impairment or destruction of the target cells (see paragraph [036]). Further, the specification teaches that the photosensitizing compound is nontoxic to the subject prior to irradiation or in its photodegraded form, and absorbs light in a range of 500-1100 nm (paragraph [036]), whereby the photosensitizing compound is activated and generates singlet oxygen and other reactive species that have biological effects resulting in damage to the endothelial membranes and ultimately to clotting the neovasculature (see paragraph [005]). Thus, the instant application describes the necessary common attributes of the photosensitizing compounds useful in the claimed conjugates. One skilled in the art can select as a photosensitizing agent for use in the conjugate of the claimed methods those compounds that are nontoxic to the subject prior to irradiation or in its photodegraded form, that absorb light in a range of 500-1100 nm, and where upon absorbing light in this range the photosensitizing compound is activated and generates

singlet oxygen and other reactive species that have biological effects resulting in damage to the endothelial membranes.

ii. Targeting Moieties

The Examiner alleges that the specification does not adequately describe the "conjugate genus" to be used in the methods because the specification fails to describe the structural features of the targeting moiety that are common to the genus. Applicant respectfully disagrees. The instant specification teaches that the targeting moiety can include specific receptors and/or antigens present on abnormal endothelium or specific ligands and/or antibodies that are themselves bindable to endothelial receptors and antigens (for example, see paragraph [014]). Thus, the genus "targeting moiety" includes any receptor and/or antigen present on abnormal endothelium as well as any ligand and/or antibody that selectively binds to endothelial receptors and antigens (see paragraph [032]). The "genus" encompasses the exemplified species and other species that are similar in function to the exemplified species.

The common "structural" feature of all of the "targeting moieties" is their ability to selectively interact with abnormal endothelium in relation to non-target tissue. The specification teaches that the targeting moiety can be any molecule or compound that binds specifically to abnormal endothelium, for example upregulated receptors or receptors on abnormal blood vessel walls (see paragraph [042]). For example, as previously presented, at the time the application was filed, many endothelial receptors were known, including VEGF receptors, αvβ3 integrins, the extra-domain B (ED-B) of fibronectin, endothelial-leukocyte adhesion molecule (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and the selectins. Similarly, the ligands that bind to these receptors also were known, such as VEGF for VEGF receptors, fibrinogen and fibronectin for αvβ3 integrins, LFA-1 for ICAM-1 and VLA-4 for VCAM-1. The specification also teaches that the targeting moiety can include antibodies that are bindable to endothelial receptors or to endothelial antigens (see paragraph [032]). Thus, one of skill in the art would recognize as one common element of the claimed targeting moiety its specificity or high degree of affinity for abnormal endothelium in relation to non-target tissue. Given the teaching of the specification and what was known in the art at the time of the effective filing date of the claims, the skilled artisan could select a targeting moiety for use in the conjugate

of the claimed method such that the targeting moiety selectively or preferentially targets abnormal endothelium in relation to non-target tissue.

c. Representative Number of Species

i. Photosensitizing Agents Provided

The specification provides a representative number of examples explicitly (17 by compound family, including porphyrins, purpurin, chlorins, bacteriochlorophylls, phthalocyanines, merocyanines, psoralens, benzoporphyrin derivatives, porfimer sodium, δ-aminolevulinic acid, pyropheophorbides, texaphyrins, verteporfin, indocyanine green, methylene blue, and toluidine blue) and two by specific tradename (PHOTOPHRIN® and FOSCAN®) and implicitly by defining the properties requisite for activity in photodynamic therapy. The specification directs the skilled artisan to a comprehensive listing of photosensitizing compound (for example, see paragraph [036], which directs one skilled in the art to Kreimer-Birnbaum, Sem. Hematol. 26:157-73, 1989). The applicant provides specific working examples that include three different photosensitizing compounds (verteporfin [054], benzoporphyrin [058], and texaphyrin [061]). Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed.

ii. Targeting Moieties Provided

The Examiner alleges that the specification discloses as species of "targeting moiety" only one ligand (ED-B of fibronectin), one specific binding pair (VEGF that binds to a VEGF receptor) and one antibody (antibody to the ED-B of fibronectin), and alleges that such a disclosure is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

First, it is noted that the original claims are part of the specification. Thus, the specification teaches as "species" of targeting moiety a first component of a bindable pair where the second component of the bindable pair is a receptor present on abnormal endothelium; a ligand bindable to a receptor present on abnormal endothelium; an antigen present on abnormal endothelium; and an antibody bindable to antigen present on abnormal endothelium. The specification also teaches as a targeting moiety the ED-B domain of fibronectin; an antibody specifically elicited to the ED-B domain of fibronectin; VEGF; a VEGF receptor; and an $\alpha v\beta 3$ integrin receptor.

The specification also provides a representative number of examples of receptors, antigens, ligands and antibodies of the binding pair explicitly (including VEGF, VEGF receptor, αvβ3 integrin receptor, CEA antigen, antibody to the extra-domain B of fibronectin, such as L19, antibody to αvβ3, such as LM609, antibody to CEA, and bispecific antibody construct that is a combination of ligand and receptor (see paragraphs [021], [043], [044] and [061]) and implicitly (such as antibodies and antibody fragments that bind to abnormal vascular endothelial receptors, and antibodies and antibody fragments that bind to upregulated vascular endothelial receptors). The specification defines the properties requisite for activity (binding to an upregulated endothelial receptor or an endothelial receptor found on an abnormal blood vessel wall). The applicant provides specific working examples that include four different ligands (ED-B of fibronectin [054], VEGF [058], αvβ3 integrin [061], and carcinoembryonic antigen [063]) and 2 receptors (VEGF receptor [059] and αvβ3 integrin [061]). Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed.

4. The Intensity of Light

The Examiner alleges that the specification provides insufficient guidance as to the intensity of light used for the claimed method "given the infinite number of undisclosed targeted photosensitizing compounds." Applicant respectfully disagrees. The specification teaches that the intensity of light is selected to be sufficient for the light to reach the target tissue yet limited to avoid over-treating the subject (for example, see paragraph [038]). Thus, an upper limit for the intensity of light is selected so that no damage to non-target tissue occurs. The specification further discloses, for example, using an intensity of light substantially less that 500 mW/cm^2 and increasing the amount of time the target is exposed to the irradiation so that a greater amount of total energy or fluence may be used without increasing the amount of the intensity of the light used (see paragraph [050]. Thus, the specification teaches that the claimed subject matter uses a combination of a selected intensity of light, for example, less than 500 mW/cm^2, administered over a period of time selected to achieve a total fluence of irradiation that is sufficiently high to activate the photosensitizing agent, as applicable, with a concomitant reduction in the intensity of

light required for activation (see paragraphs [053] and [057]). The specification teaches that the duration of illumination will be determined empirically but is preferably a total or cumulative period of time between 4 minutes and 148 hours (see, *e.g.*, paragraph [048]). The specification teaches that the total fluence of the light is between 30 Joules and about 25,000 Joules (see, *e.g.*, paragraph [049]). The specification provides exemplary combinations of intensity of light and duration of illumination. For example, the specification discloses using an intensity of 250 mW/cm^2 light to irradiate a subject for approximately 1 hour over the course of one or more sessions to provide a total fluence of 900 J/cm^2 (see, e.g. paragraph [066]. The specification also discloses irradiating a subject in one or more sessions for a total period of 10 minutes with light having an intensity of 400 mW/cm^2 and a wavelength of 690 nm, resulting in a total fluence of 240 $Joules/cm^2$ (see, e.g., paragraph [055]). Therefore, in light of the teachings of the specification and what is known to those skilled in this art, the specification provides sufficient guidance for selecting the intensity of the light to be used in the claimed method.

i. Alleged Lack of Upper Limit of Illumination

The Examiner alleges that even if the photosensitizing compound is enabled, the light source, the combination of the intensity of light used for the step of illumination and the duration of illumination to arrive at the total fluence "are critical for the claimed method" and that "given the lack of an upper limit for the duration of illumination, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues." Applicant respectfully disagrees. The specification teaches at paragraphs [013] - [016] that:

> The present invention describes methods to treat neovascular disease of the eye based on the precise targeting of photosensitive compounds to target tissue and the activation of these targeted photosensitizer compounds by subsequently administering to the subject non-coherent (non-laser) or coherent (laser) light of a relatively low fluence rate over a prolonged period of time.
>
> The present invention further discloses the selective binding of the photosensitizing agent to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens. This targeting scheme decreases the amount of sensitizing drug required for effective therapy, which in turn reduces the fluence rate or light irradiation needed for effective photoactivation. As a result, the

> disclosed method achieves maximal dosage to abnormal endothelium with minimal side effects or collateral tissue damage.
>
> Additionally, the present disclosure teaches the unexpected use of a low power non-coherent light source utilized for longer than about 4 minutes. This teaches away from the use of a high powered, brief exposure using laser light, results in fuller, more efficient activation of the bound photosensitizers, and enables a high therapeutic index using a low dose drug. Moreover, a low power non-coherent light source is relatively inexpensive and simpler to use. Finally, because the present invention teaches photoactivation with a non-coherent, broadband light source, different types of photosensitizers can be activated with a single light source.
>
> Due to the highly specific nature of the photosensitizer uptake, excess light or light falling on nonpathologic areas causes no unwanted photoactivation. Therefore, a region of the retina or macular with diffuse abnormalities can be safely treated without damaging intervening normal eye structures. In addition, eye movement by the patient during treatment, which can result in the further exposure to light of normal eye structures, is harmless. Thus, the use of highly targeted photosensitizers allows the delivery of light in a diffuse fashion and over a prolonged illumination period. In fact, one embodiment of the invention is the use of ambient light to activate the photosensitized neovascular tissue.

Thus, the specification discloses that selection of a combination of a low intensity light and a prolonged duration of irradiation to activate the photosensitizer reduces the potential for damage to non-target tissue exposed to the irradiation. Contrary to the Examiner's assertion, there is an upper limit for the intensity of light used. The claimed subject matter requires a selection of a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Thus, an upper limit for the intensity of light used it that which results in destruction of neovascular target tissue without damaging the non-target tissue through which the light passes. The specification teaches, for example, at paragraph [050], that a reduction in the intensity of light used is achieved by a concomitant increase in the duration of irradiation used.

The instant application recognizes the need for a method of photodynamic therapy that reduces the risk of damage to non-target tissues and yet can be used to effectively treat target tissues such as abnormal endothelium. It is only the instant

application that teaches the significance and applicability of alteration of two particular treatment parameters, i.e., the intensity of light and the duration of irradiation, in combination with the use of a targeted photoreactive conjugate in achieving the needed method without limiting the number and types of photoreactive compounds that may used in the method. As described in the instant application, these parameters are selected to provide for a relatively high total fluence of radiation that is sufficiently high to activate the photosensitizing agent using a relatively low intensity of light.

The optimal total fluence can be determined empirically, for example, in a light dose escalation trial. The high total fluence is administered in such a way that no collateral damage is incurred by non-target or normal tissue. For example, the instant application teaches that the total fluence can be achieved by administering light at a relatively low fluence rate or intensity for a prolonged period of time. The instant specification teaches that the intensity must be sufficient for the radiation to reach the target tissues. The duration must be sufficient to photoactivate enough photosensitive compound to achieve the desired effect on the target site. Thus, the instant application teaches the types of alterations of the parameters of radiation administration that can be used to achieve activation of targeted photosensitive conjugates in target tissues for destruction of target tissues, and in particular, abnormal endothelium, without collateral damage to non-target tissues. Hence, one skilled in this art, in light of the teachings of the specification, would be able to select a combination of light intensity and a duration of irradiation to activate the photosensitizer while avoiding any damage to non-target tissue. Therefore, it is respectfully submitted that the skilled artisan would recognize that applicant "had possession" of the claimed subject matter.

5. Alleged Missing Step

The Examiner contends that there is insufficient written description of the claimed methods because that the method step of allowing non-specifically bound photosensitizing compound to clear from collateral tissues is missing in the claims. The applicant respectfully submits that the pending claims include as an element allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Applicant respectfully submits that the rejection be reconsidered and withdrawn.

REJECTION OF CLAIMS 1-9, 11-12, 16-24, 36 and 38-41 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - ALLEGED NEW MATTER

Claims 1-6, 11-12, 16-24, 36 and 38-49 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner alleges that the amendments to claims 1, 18-22 and added claims 45 and 46 represents a departure from the specification and claims as originally filed.

This rejection is respectfully traversed.

RELEVANT LAW

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, s/he was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265 (CCPA 1976).

THE CLAIMS

Claim 1 is directed to a method to treat neovascular disease of the eye that includes administering a conjugate comprising a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the

photosensitizing compound for a period of time sufficient to activate the photosensitizing compound; where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Claim 18 depends from claim 1, and is directed to an embodiment where the photosensitized neovascular tissue is illuminated for at least 4 minutes.

Claim 19 depends from claim 1, and is directed to an embodiment where the photosensitized neovascular tissue is illuminated for at least 20 minutes.

Claim 20 depends from claim 1, and is directed to an embodiment where the photosensitized neovascular tissue is illuminated for at least 1 hour.

Claim 21 depends from claim 1, and is directed to an embodiment where the photosensitized neovascular tissue is illuminated for at least 24 hours.

Claim 22 depends from claim 1, and is directed to an embodiment where the neovascular tissue is treated with a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2.

Claim 45 depends from claim 1, and is directed to an embodiment where a combination of an intensity of light of less than 500 mW/cm^2 and a duration of illumination of at least 4 minutes is selected to produce a total fluence of light irradiation from between about 30 J/cm^2 to about 25,000 J/cm^2.

Claim 46 is directed to a method to treat neovascular disease of the eye that includes administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovascular tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged, where the neovascular tissue is treated with a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2.

ANALYSIS

Claim 1

The Examiner alleges that the recitation "at least in part with the characteristic light absorption wavelength of the photosensitizing compound" in claim 1 represents a departure from the specification and claims as originally filed as the application allegedly does not provide clear support for this phrase. It is respectfully submitted that, at the time of application, applicant appreciated and was in possession of a method of photodynamic therapy that includes as a step illuminating the neovascular tissue with light including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound, as instantly claimed. The specification provides basis for the recitation. For example, specific basis for the recitation in question can be found at paragraph [049], which recites:

> [049] Preferably, the total fluence or energy of the light used for irradiating, as measured in Joules, is between about 30 Joules and about 25,000 Joules; more preferably, between about 100 Joules and about 20,000 Joules; and most preferably, between about 500 Joules and about 10,000 Joules. Light having a waveband corresponding at least in part with the characteristic light absorption waveband of said photosensitizing agent is used for irradiating the target issue. [emphasis added]

Thus, the recitation "corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound" has basis in the original disclosure and complies with the written description requirement of 35 U.S.C. §112. Hence, the recitation "corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound" does not introduce new matter because the specification as filed discloses this embodiment of the claimed subject matter. Therefore, because this recitation is subject matter that is supported by or conforms to the disclosure of the application as filed, the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

Claims 18-21

The Examiner alleges that pending claims 18-21 represent a departure from the specification and claims as originally filed because an upper limit is not specified in pending claims 18-21. The Examiner alleges that the specification teaches an upper limit at paragraph [048]. It is respectfully submitted that, at the time of filing of the

instant claims and parent application, applicant appreciated and was in possession of a method of photodynamic therapy where the photosensitized neovascular tissue is illuminated for at least 4 minutes, for at least 20 minutes, for at least 1 hour and for at least 24 hours, as instantly claimed in claims 18-21, respectively. Claims 18-21 as originally filed recite:

18. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 4 minutes.

19. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 20 minutes.

20. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 1 hour.

21. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 24 hours.

The original claims are part of the specification (MPEP 608.01(l)). None of original claims 18-21 specifies an upper limit. Thus, pending claims 18-21 are directed to subject matter having basis in the original disclosure and these claims comply with the written description requirement of 35 U.S.C. §112. No new mater is added. Therefore, the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

Claims 22 and 46

The Examiner alleges that pending claims 22 and 46 represents a departure from the specification and claims as originally filed because the specification allegedly does not provide clear support for the narrow range between about 240 J/cm^2 to about 900 J/cm^2. Applicant respectfully submits that, at the time of the effective filing date of the claims, applicant appreciated and was in possession of a method of photodynamic therapy where the neovascular tissue is treated with a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2. Claim 22 as originally filed recites:

22. The method of claim 1, wherein the neovascular tissue is treated with a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2.

The original claims are part of the specification (MPEP 608.01(l)). Original claim 22 clearly recites a range of irradiation from between about 240 J/cm^2 to about 900 J/cm^2. Thus, pending claims 22 and 46 are directed to subject matter having basis in the original disclosure and complies with the written description requirement of 35

U.S.C. §112. No new matter is added. Therefore, the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

Claim 45

The Examiner alleges that pending claim 45 represents a departure from the specification and claims as originally filed because an upper limit is not specified. It is respectfully submitted that, at the time of application, applicant appreciated and was in possession of a method of photodynamic therapy where the photosensitized neovascular tissue is illuminated for at least 4 minutes, as instantly claimed. Basis for this element can be found in original claim 18, which includes the recitation "wherein the photosensitized neovasculature is illuminated ***for at least 4 minutes***" [emphasis added]. The original claims are part of the specification (MPEP 608.01(l)). Original claim 18 does not specify an upper limit and provides basis for the subject matter claimed in claim 45. No new matter is added. Thus, pending claim 45 is directed to subject matter having basis in the original disclosure and complies with the written description requirement of 35 U.S.C. §112. Therefore, the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

THE REJECTION OF CLAIMS 1, 3-6, 11, 12, 17-21, 36 and 41-43 UNDER 35 U.S.C. §102(b)

Claims 1, 3-6, 11, 12, 17-21, 36 and 41-43 are rejected under 35 U.S.C. § 102 as anticipated by Strong *et al.* (U.S. Patent No. 5,756,541) because Strong *et al.* allegedly discloses a method to treat neovascular disease of the eye such as age-related macular degeneration that includes administering a photosensitizing compound such as a chlorin and green porphyrin coupled to a specific binding ligand such as an antibody that binds to the target ocular tissue. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be

found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention.

THE CLAIMS

See related section above.

Disclosure of Strong *et al.*

Strong *et al.* discloses a photodynamic therapy of the eye to reduce unwanted neovasculature, especially neovasculature of the choroid (col. 2, lines 1-3). Strong *et al.* discloses that its green porphyrins strongly interact with lipoproteins (col. 3, lines 53-56). Strong *et al.* discloses coupling the photosensitizer to a target-specific ligand such as an antibody or an immunologically active fragment or formulating it in a liposome (col. 4, lines 8-16). Strong *et al.* discloses that fluence during the irradiating treatment varies from about 50-200 J/cm^2 (col. 4, lines 56-59), and that irradiance varies from about 150-900 mW/cm^2 (col. 4, lines 60-64). Strong *et al.* discloses waiting a "suitable time period to permit an effective concentration of the compound to accumulate in the desired region of the eye" (col. 2, lines 27-29) and to "localize in the eye" (co. 2, line 10). Strong *et al.* discloses administering light from a coherent argon dye laser (col. 5, lines 45-51). Strong *et al.* discloses that its treatment results in deleterious effects of the tissue immediately surrounding the activated photosensitizer (col. 2, lines 31-33), such as mild retinal whitening in some cases (col. 5, lines 10-13). Strong *et al.* discloses that there is a nexus between the type of photoactive agent, the formulation, the mode of administration, and the dosage level and discloses adjusting these parameters (col. 4, lines 8-16). Strong *et al.* discloses that the dose should be adjusted with respect to fluence, irradiance, duration of the light used in photodynamic therapy, and time interval between administration of the dose and the therapeutic irradiation (col. 4, lines 24-30). Strong *et al.* discloses that the fluence during irradiation treatment can vary widely depending on the type of tissue, depth of target tissue and the amount of overlying fluid or blood (col. 4, lines 56-59).

Differences between the claimed subject matter and the disclosure of Strong *et al.*

Strong *et al.* does not disclose affirmatively selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-target tissue through which the light passes. Strong *et al.* teaches at col. 4, lines 22-33 that:

> The various parameters used for effective, selective photodynamic therapy in the invention are interrelated. Therefore, the dose should also be adjusted with respect to other parameters, for example, fluence, irradiance, duration of the light used in photodynamic therapy, and time interval between administration of the dose and the therapeutic irradiation. All of these parameters should be adjusted to produce significant enhancement of visual acuity without significant damage to the eye tissue.
>
> Stated in alternative terms, as the photoactive compound dose is reduced, the fluence required to close choroidal neovascular tissue tends to increase.

Thus, Strong *et al.* discloses that the dose of the photosensitizing agent should be adjusted with respect to fluence, irradiance, duration of illumination and the time interval between administration of the dose and the irradiation. Strong *et al.* restated the disclosure directed to varying the photodynamic therapy parameters to state that as the photoactive compound dose is reduced, the fluence required to close choroidal neovascular tissue tends to increase. There is no disclosure in Strong *et al.* that combinations of the parameters of intensity of light and duration of illumination can be determined empirically that provide for a total fluence that achieves destruction of a target tissue without damage to a non-target tissue through which the light passes. Instead, Strong *et al.* discloses that all of the photodynamic therapy parameters (fluence, irradiance, duration of the light used in photodynamic therapy, and time interval between administration of the dose and the therapeutic irradiation) should be adjusted relative to the dose level administered. Further, Strong *et al.* discloses that selection of a fluence is determined by the type of tissue to be treated, depth of target tissue and the amount of overlying fluid or blood. The reference also discloses that the irradiance typically varies from about 150-900 mW/cm^2 and that higher irradiances may be selected to shorten the treatment times (col. 4, lines 60-64). Claim 1 of Strong *et al.* includes as an element "wherein said radiation is conducted for a time and at an intensity sufficient to improve visual acuity in said subject." There is nothing in the disclosure of Strong *et al.* directed to

selecting combinations of the parameters of intensity of light and duration of illumination to provide a total fluence that achieves destruction of a target tissue without damage to a non-target tissue through which the light passes.

The instant application recognizes the need for a method of photodynamic therapy that reduces the risk of damage to non-target tissues and yet can be used to effectively treat target tissues such as abnormal endothelium. It is only the instant application that discloses the significance and applicability of alteration of two particular treatment parameters, i.e., the intensity of light and the duration of irradiation, in combination with the use of a targeted photoreactive conjugate in achieving the needed method without limiting the number and types of photoreactive compounds that may used in the method. As described in the instant application, these parameters are selected to provide for a relatively high total fluence of radiation that is sufficiently high to activate the photosensitizing agent. The optimal total fluence can be determined empirically, for example, in a light dose escalation trial. The high total fluence is administered in such a way that minimal to no collateral damage is incurred by non-target or normal tissue. For example, the total fluence can be achieved by administering light at a relatively low fluence rate or intensity for a prolonged period of time. The intensity is selected to be sufficient for the radiation to reach the target tissues. The duration is selected to be sufficient to photoactivate enough photosensitive compound to achieve the desired effect on the target site. Thus, only the instant application discloses the types of alterations of the parameters of intensity of light used for the step of illumination and the duration of illumination that can be used to achieve activation of targeted photosensitive conjugates in target tissues for destruction of target tissues, and in particular, abnormal endothelium, without collateral damage to non-target tissues.

Indeed, Strong *et al.* discloses that its method results in deleterious effects of the tissue immediately surrounding the activated photosensitizer, making no distinction between target and non-target tissue, and discloses that mild retina whitening occurs (see, *e.g.*, col. 2, lines 31-33 and col. 5, lines 10-13). Hence, Strong *et al.* does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Thus, Strong *et al.* does not disclose every element of claim 1. Because Strong *et al.* does not disclose every element of claim 1, Strong *et al.* does not anticipate claim 1. Because claims 3-6, 17-21, 36 and 41-43 depend from claim 1, Strong *et al.* does not anticipate any of the pending claims. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Rebuttal to Examiner's Arguments

Claimed Method Allegedly No Different than Method of Strong *et al.*

The Examiner alleges that the instantly claimed method "is no different than the method of '541 patent because the specific wavelength, the duration and total fluence are not recited in the claim" (see Office Action page 21). Applicant respectfully disagrees. As discussed above, the instant claims include as an element "a combination of an intensity of light used for the step of illumination and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged." Strong *et al.* does not disclose as an element of its method selecting a combination of an intensity of light used for the step of illumination and a duration of illumination to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Thus, the instant claims are different from the disclosure of Strong *et al.* Strong *et al.* does not disclose every element of the claimed method. It is irrelevant that a specific wavelength, a specific duration or a specific total fluence are not recited in the instant claim. Applicant respectfully submits that a specific wavelength, a specific duration and a specific total fluence are not required for patentability of the claimed method.

Claim 5

Applicant respectfully submits that claim 5 is directed to an embodiment of the method of claim 1 where the treated neovascular disease is diabetic retinopathy. Strong *et al.* does not disclose treating diabetic retinopathy. Thus, as applied to claim 5, the rejection is without merit and should be withdrawn.

THE REJECTION OF CLAIMS 1, 3-6, 11, 18, 36, 42, 43 AND 45 UNDER 35 U.S.C. §102(b)

Claims 1, 3-6, 11, 18, 36, 42, 43 and 45 are rejected under 35 U.S.C. § 102(b) as anticipated by Kramer *et al.* (Ophthalmology 103(3): 427-38) because Kramer *et*

al. allegedly discloses a method to treat unwanted choroidal neovasculature such as diabetic retinopathy, age-related macular degeneration, corneal neovascularization and ocular tumor that includes administering a photosensitizing compound such as a benzoporphyrin derivative or verteporfin conjugated to a targeting moiety such as a liposome or LDL that selectively binds to LDL receptor or rapidly proliferating endothelium of the eye, allowing non-bound conjugate to clear from non-target tissue, and illuminating with light that matches the absorption wavelength of the photosensitizing compound.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above.

Disclosure of Kramer *et al.*

Kramer *et al.* discloses a photodynamic therapy of the eye to reduce unwanted neovasculature that includes administering liposomal verteporfin as a photosensitizer (see page 434. col. 2., second full paragraph). The method includes irradiation with laser light with an irradiance of 600 mW/cm^2 and fluence of 150 J/cm^2 (see page 427, second paragraph). Kramer *et al.* discloses complexing benzoporphyrin derivative (BPD) with low-density lipoprotein to enhance its delivery to neovascular and tumor tissues because of increased LDL receptors in rapidly proliferating endothelium (page 428, col. 1, second full paragraph). The reference also discloses delivery of BPD in liposomal delivery systems (page 428, col. 1, third full paragraph). Kramer *et al.* discloses adjusting dye dose and time of laser irradiation after dye injection to minimize damage to retina and choroids (page 437, col. 1, first full paragraph). Kramer *et al.* discloses that reducing the dye dose resulted in more selective closure of the choriocapillaries with minimal damage to the adjacent tissues (page 434, col. 1, second full paragraph). Kramer *et al.* discloses that photodynamic therapy using a dye dosage of 1 mg/kg led to damage of both inner and outer retina and that irradiation within 50 minutes after dye injection demonstrated grade 5 damage and lesions irradiated 60 minutes or more after dye injection demonstrated grade 4 damage (page 434, col. 1, third full paragraph). Kramer *et al.* discloses treatments of normal retina and choroids using its methods resulted in damage graded 1 to 3, which

the reference states is believed to be acceptable damage although long-term studies are required to study recovery and extent to which such damage might affect visual function (page 435, bridging paragraph of cols. 1-2). Kramer discloses that reducing the dye dose increased treatment selectivity and shortened the time interval after dye injection in which laser irradiation leads to successful closure of CNV (page 435, col. 1, second full paragraph).

Differences between the claimed subject matter and the disclosure of Kramer *et al.*

Kramer *et al.* does not disclose affirmatively selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-target tissue through which the light passes. There is no disclosure in Kramer *et al.* that combinations of the parameters of intensity of light and duration of illumination can be determined empirically that provide for a total fluence that achieves destruction of a target tissue without damage to a non-target tissue through which the light passes. Instead, Kramer *et al.* discloses that collateral tissue damage can be reduced in its methods by reducing the dye dose used in its photodynamic therapy.

Indeed, Kramer *et al.* discloses that its method results in damage of both inner and outer retina, and that treatments of normal retina and choroids using its methods resulted in damage graded 1 to 3, which the reference states is believed to be acceptable damage although long-term studies are required to study recovery and extent to which such damage might affect visual function. Hence, Kramer *et al.* does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Thus, Kramer *et al.* does not disclose every element of claim 1. Because Kramer *et al.* does not disclose every element of claim 1, Kramer *et al.* does not anticipate claim 1. Because claims 3-6, 11, 18, 36, 42, 43 and 45 depend from claim 1, Kramer *et al.* does not anticipate any of the pending claims. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REJECTION OF CLAIMS 1, 2, 11 and 38-40 UNDER 35 U.S.C. §103(a)

Claims 1, 2, 11 and 38-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strong *et al.* (U.S. Patent No. 5,756,541) as evident by Kramer *et al.* (Ophthalmology 103(3): 427-38) in view of Boulton *et al.* (*Br. J Opthalmol 82*: 561-568, 1998), Blaauwgeers *et al.* (*Am J Pathology 155(2)*: 421-428, 1999), Klyashchitsky *et al.* (*J of Controlled Release 29(1-2)*: 16-16, 1994) and Prewett *et al.* (*Cancer Res 59*: 5209-18, 1999) because although Strong *et al.* does not teach non-laser light, or binding the photosensitizer to a targeting moiety that is VEGF bindable to a VEGF receptor or an antibody that binds to a VEGF receptor or a VEGF receptor, Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* allegedly cure these defects.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

The claims are discussed above.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teachings of Strong *et al.* are discussed above.

Boulton *et al.*

Boulton *et al.* teaches that VEGF is generally absent from normal retina and that staining of tissue using anti-VEGF antibody shows VEGF in most diabetic tissue, but that this was dependent on both the specificity of the antibody used and the category of the tissue (page 561, col. 1., lines 24-29). Boulton *et al.* teaches that some anti-VEGF antibodies also associated with extravascular components of the inner retina (page 561, col. 1, lines 33-35). The reference teaches that VEGF staining correlated with active neovascularization and that VEGF may play a role in diabetic retinopathy (page 566, col. 1, lines 48-56). Boulton *et al.* teaches laser photocoagulation (page 567, col. 1, lines 26-31).

Boulton *et al.* does not teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Boulton *et al.* does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Blaauwgeers *et al.*

Blaauwgeers *et al.* teaches that the retinal pigment epithelium monolayer is involved in the pathogenesis of choroidal neovascularization such as in age-related macular degeneration (page 421, col. 2, lines 13-16). Blaauwgeers *et al.* teaches that up-regulated basolateral VEGF secretion or loss of polarity of VEGF production may play a role in the pathogenesis of choroidal neovascularization (page 421, col. 2, lines 3-9). The reference teaches that defects in the retinal pigment epithelium monolayer could lead to misdirection of secreted VEGF and subsequent classical subretinal neovascularization (page 428, col. 1, lines 1-4).

Blaauwgeers *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Blaauwgeers *et al.* does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Blaauwgeers *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Klyashchitsky *et al.*

Klyashchitsky *et al.* teaches that photodynamic therapy is based on the ability of porphyrins and some other photosensitizers to accumulate preferentially in tumor cells and to generate singlet oxygen when activated by visible light (page 1, abstract). Klyashchitsky *et al.* teaches targeted photosensitizers using targeting moieties having high affinity to the tumor-associated antigen or receptor (page 2, col. 2, lines 21-26). Klyashchitsky *et al.* teaches that such targeting moieties include monoclonal antibodies, liposomes, low density lipoproteins and lectins (page 2, col. 1, lines 24-33).

Klyashchitsky *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Klyashchitsky *et al.* does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Klyashchitsky *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Prewett *et al.*

Prewett *et al.* teaches that tumor angiogenesis is mediated by tumor-secreted growth factors that interact with their surface receptors expressed on endothelial cells, and that VEGF and the VEGF receptor play a role in vascular permeability and tumor angiogenesis (page 5209, col. 1, lines 1-5). Prewett *et al.* teaches that anti-VEGF receptor antibody treatment of tumors results in decreased microvessel density, tumor cell apoptosis, decreased tumor cell proliferation and extensive tumor

necrosis (page 5209, col. 1, lines 23-29). The reference teaches that VEGF and VEGF receptors are implicated in angiogenesis that occurs in many human solid tumors (page 5209, col. 2, lines 25-27), and that blocking the VEGF receptor with anti-VEGF receptor antibodies inhibits angiogenesis (page 5214, col. 2, lines 9-12). Prewett *et al.* teaches that neutralizing soluble VEGF receptor or Flk-1/KDR kinase inhibitors inhibited angiogenesis and tumor growth (page 5209, col. 2, lines 33-37).

Prewett *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Prewett *et al.* does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Prewett *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following.

The combination of teachings of Strong *et al.* with the teachings of Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* does not result in the instantly claimed methods.

Independent claim 1 and its dependent claims include as subject matter administering a therapeutically effective amount of a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular target tissue with light using a non-coherent light source including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound, where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the

light passes remains undamaged. As discussed above in the traverse under §102, above, Strong *et al.* does not teach or suggest selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Boulton *et al.* does not cure this defect. Boulton *et al.* does not teach or suggest the parameters of the intensity or duration of light used for photodynamic therapy, and thus Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Boulton *et al.* teaches that VEGF plays a role in neovascularization in diabetic retinopathy, Boulton *et al.* does not teach or suggest the subject matter missing from Strong *et al.* Thus, the combination of the teachings of Strong *et al.* and Boulton *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Blaauwgeers *et al.* does not cure this defect. Blaauwgeers *et al.* does not teach or suggest any intensity or duration of light to be used for photodynamic therapy, nor selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Thus, combining the teachings of Blaauwgeers *et al* with Strong *et al.* or with the combination of Strong *et al.* and Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Blaauwgeers *et al.* teaches that the loss of polarity of VEGF production may play a role in the pathogenesis of choroidal neovascularization, the combination of the teachings of Blaauwgeers *et al.* with Strong *et al.* or with the combined teachings of Strong *et al.* and Boulton *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Klyashchitsky *et al.* does not cure this defect. Klyashchitsky *et al.* teaches targeting photosensitizers to tumors using monoclonal antibodies, liposomes, low

density lipoproteins and lectins that have high affinity to a tumor-associated antigen or receptor. Klyashchitsky *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Klyashchitsky *et al.* teaches targeted photosensitizers, combining the teachings of Klyashchitsky *et al.* with the teachings of Strong *et al.*, or the combined teachings of Strong *et al.* and Boulton *et al.*, or the combined teachings of Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* fails to teach or suggest every element of claim 1 and its dependent claims.

Prewett *et al.* does not cure this defect. Prewett *et al.* teaches that VEGF and the VEGF receptor play a role in vascular permeability and tumor angiogenesis and that anti-VEGF receptor antibody treatment of tumors results in decreased microvessel density and tumor necrosis. Prewett *et al.* does not teach or suggest any intensity or duration of light to be used for photodynamic therapy, nor does the reference teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Prewett *et al.* teaches that blocking the VEGF receptor with anti-VEGF receptor antibodies inhibits angiogenesis, combining the teachings of Prewett *et al.* with the teachings of Strong *et al.*, or with the combined teachings of Strong *et al.* and Boulton *et al.*, or with the combined teachings of Strong *et al.*, Boulton *et al.* and Blaauwgeers *et al.*, or with the combined teachings of Strong *et al.*, Boulton *et al.*, Blaauwgeers *et al.* and Klyashchitsky *et al.*, fails to teach or suggest every element of claim 1.

Thus, the combination of the teachings of Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* and Klyashchitsky *et al.* and Prewett *et al.* does not result in the subject matter of claims 1, 2, 11 and 38-40. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

REBUTTAL TO EXAMINER'S ARGUMENTS

In maintaining this rejection, the Examiner alleges that Applicant's previous argument was unpersuasive because the references were individually "attacked"

instead of addressing the combination of the references. The Applicant respectfully disagrees.

It is noted the previous response did address the combination of the teachings of the references and did not "attack" them individually. Attention is directed to the section at page 47 of the previous response with the header "ANALYSIS" and the header "The combination of teachings of Strong *et al.* with the teachings of Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* does not result in the instantly claimed methods," which states in part:

> Independent claim 1 and its dependent claims include as subject matter administering a therapeutically effective amount of a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular target tissue with light using a non-coherent light source including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound, where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. As discussed above in the traverse under §102, Strong *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, nor selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.
>
> Boulton *et al.* does not cure these defects. Boulton *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, and thus Boulton *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, nor does the reference teach or suggest the parameters of the intensity or duration of light used for photodynamic therapy. Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Boulton *et al.* teaches that VEGF plays a role in neovascularization in diabetic retinopathy, the combination of the teachings of Strong *et al.* and Boulton

et al. does not teach or suggest every element of claim 1 and its dependent claims.

Applicant respectfully submits that the individual references were not "attacked," but instead the references were analyzed to show that the elements missing from Strong *et al.* are not taught or suggested in any of Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* or Prewett *et al.*, alone or in any combination.

REJECTION OF CLAIMS 1, 11 and 43 UNDER 35 U.S.C. §103(a)

Claims 1, 11 and 43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strong *et al.* (U.S. Patent No. 5,756,541) as evident by Kramer *et al.* in view of Blumenkranz *et al.* (U.S. Patent No. 6,270,749) because Strong *et al.* allegedly teaches every element of the claimed subject matter except an antibody bindable to an antigen such as VEGF present on abnormal endothelium as a targeting moiety and texaphyrin as a photosensitizing compound, but Blumenkranz *et al.* allegedly cures this defect. The Examiner contends that Blumenkranz *et al.* teaches a conjugate including lutetium texaphyrin or benzoporphyrin derivatives conjugated to a monoclonal antibody to VEGF on abnormal endothelium. The Examiner contends that it would have been obvious to substitute the photosensitizing compounds and targeting moieties of Blumenkranz *et al.* for the photosensitizing compounds taught in Strong *et al.* for targeting the photosensitive compound to neovasculature tissue in the eye.

This rejection is respectfully traversed.

RELEVANT LAW

The relevant law is discussed above.

THE CLAIMS

See related section above.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teachings of Strong *et al.* are discussed above.

Blumenkranz *et al.*

Blumenkranz *et al.* teaches using texaphyrin for carrying out angiography and photodynamic therapy of the eye (col. 4, lines 7-29). Blumenkranz *et al.* teaches coupling texaphyrins to site-directing molecules to form conjugates for targeted *in vivo* delivery, where the site-directing molecule can include VEGF or a class of integrin, both of which are important in ocular angiogenesis (col. 10, lines 26-52).

Blumenkranz *et al.* teaches that the dose of the photosensitizing compound is adjusted with respect to fluence, irradiance, duration of the light used in photodynamic therapy and the time interval between administration of the dose and the therapeutic irradiation and that these parameters should be adjusted relative to dose to produce significant damage to abnormal vascular tissue without significant damage to the surrounding tissue (col. 20, lines 54-62). The reference teaches that damage to non-target tissue can be minimized by adjusting the length of time between administration of the photosensitizing compound and administration of light irradiation (col. 21, lines 37-45). Blumenkranz *et al.* teaches that the fluence and irradiance during the irradiating treatment can vary depending on type of tissue, depth of target tissue and the amount of overlying fluid or blood (col. 21, lines 22-25).

Blumenkranz *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Strong *et al.* with the teachings of Blumenkranz *et al.* does not result in the instantly claimed methods.

As discussed above, Strong *et al.* does not teach or suggest selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Blumenkranz *et al.* does not cure this defect. Blumenkranz *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. The only teaching in Blumenkranz *et al.* directed to the combination of fluence and irradiance during the irradiating treatment is that these parameters can vary depending on type of tissue, depth of target tissue and the amount of overlying fluid or blood. Blumenkranz *at al.* teaches that damage to non-

target tissue can be minimized by adjusting the length of time between administration of the photosensitizing compound and administration of light irradiation. Thus, only the instant application discloses the types of alterations of the parameters of intensity of light used for the step of illumination and the duration of illumination that can be used to achieve activation of targeted photosensitive conjugates in target tissues for destruction of target tissues, and in particular, abnormal endothelium, without collateral damage to non-target tissues.

Hence, even if, arguendo, Blumenkranz *et al.* teaches a conjugate of texaphyrin and VEGF, Blumenkranz *et al.* does not teach or suggest the element missing from Strong *et al.*, and thus the combination of the teachings of Strong *et al.* and Blumenkranz *et al.* does not teach or suggest every element of claim 1 and its dependent claims. Neither Strong *et al.* nor Blumenkranz *et al.*, alone or in combination, teaches or suggests selecting a combination of intensity of light used for irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target tissue is destroyed and the healthy non-target tissue remains undamaged. Thus, combining the teachings of Strong *et al.* and Blumenkranz *et al.* does not result in the subject matter of claims 1, 11 and 43. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 1 AND 44 UNDER 35 U.S.C. §103(a)

Claims 1 and 44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strong *et al.* (U.S. Patent No. 5,756,541) as evident by Kramer *et al.* in view of Abels *et al.* (WO 97/31582) because Strong *et al.* allegedly teaches every element of the claimed subject matter except indocyanine green as a photosensitizing compound, but Abels *et al.* allegedly cures this defect. The Examiner contends that Abels *et al.* teaches that indocyanine green (ICG) is effective in destroying irradiated tissue and eliminating proliferating cancer cells without inducing scarring. The Examiner contends that it would have been obvious to substitute the photosensitizing compound ICG of Abels *et al.* for the photosensitizing compounds taught in Strong *et al.* for targeting the photosensitive compound to neovasculature tissue in the eye.

This rejection is respectfully traversed.

RELEVANT LAW

The relevant law is discussed above.

THE CLAIMS

Claim 1 is discussed above. Claim 40 is directed to an embodiment of claim 1 where the photosensitizing compound is indocyanine green.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teachings of Strong *et al.* are discussed above.

Abels *et al.*

Abels *et al.* teaches a method of treating cancer and/or a dermatological disease or condition that includes administering to a patient in need of such treatment an effective amount of indocyanine green and irradiating the affected or apparently affected tissue of the patient with a dose of light having a wavelength within the range of from 770 to 840 nm, the dose of light being effective to therapeutically treat the cancer and/or dermatological disease or condition, but preferably ineffective to thermally destroy the irradiated tissue (page 6). Abels *et al.* teaches a method for treatment of dermatological diseases and conditions which reduces the risks of scarring associated with conventional surgery and laser surgery (page 5). Abels *et al.* teaches using light doses in the range of 10 J/cm^2 to 40 J/cm^2 to avoid thermal heating or photothermal destruction (page 8). The reference teaches that laser power densities may have an effect on phototherapeutic effectiveness as compared to photothermal effectiveness, where photothermal therapy typically will employ a high power density of, for example, 10 to 20 W/cm^2 and photodynamic therapy avoids thermal heating by using a power density of less than 10 W/cm^2, such as from 5 mW/cm^2 to 5 W/cm^2, although deeper-seated tumors may be more effectively treated with a higher power density of light (e.g., 2-5 W/cm^2) (see page 8). Abels *et al.* teaches damage to surrounding normal tissue can be minimized be delaying light irradiation after administration of the ICG (see page 14).

Abels *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following.

The combination of teachings of Strong *et al.* with the teachings of Abels *et al.* does not result in the instantly claimed methods.

As discussed above, Strong *et al.* does not teach or suggest selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Abels *et al.* does not cure this defect. Abels *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Abels *et al.* teaches that damage to non-target tissue can be minimized by adjusting the length of time between administration of the photosensitizing compound and administration of light irradiation. Abels *et al.* does not teach or suggest that damage to non-target tissue can be avoided by selection of a combination of an intensity of light for illuminating and a duration of illumination. Thus, only the instant application discloses the types of alterations of the parameters of intensity of light used for the step of illumination and the duration of illumination that can be used to achieve activation of targeted photosensitive conjugates in target tissues for destruction of target tissues, and in particular, abnormal endothelium, without collateral damage to non-target tissues.

Hence, even if, arguendo, Abels *et al.* teaches using ICG as a photosensitizing compound, Abels *et al.* does not teach or suggest the element missing from Strong *et al.*, and thus the combination of the teachings of Strong *et al.* and Abels *et al.* does not teach or suggest every element of claim 1 and its dependent claims. Neither Strong *et al.* nor Abels *et al.*, alone or in combination, teaches or suggests selecting a combination of intensity of light used for irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target tissue is destroyed and the healthy non-target tissue remains undamaged. Thus, combining the teachings of

Strong *et al.* and Abels *et al.* does not result in the subject matter of claims 1 and 44. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above, reconsideration and allowance of this application is respectfully requested.

Respectfully submitted,
FISH & RICHARDSON P.C.

By: _____
Stephanie Seidman
Registration No. 33, 779

Attorney Docket No. 17105-026001 (0062)
Address all correspondence to:
Stephanie Seidman, Esq.
FISH & RICHARDSON P.C.
12390 El Camino Real
San Diego, CA 92130-2081
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
e-mail: seidman@fr.com